STEROIDAL TRANSFORMATION

THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

TO

THE ALIGARH MUSLIM UNIVERSITY, ALIGARH

BY

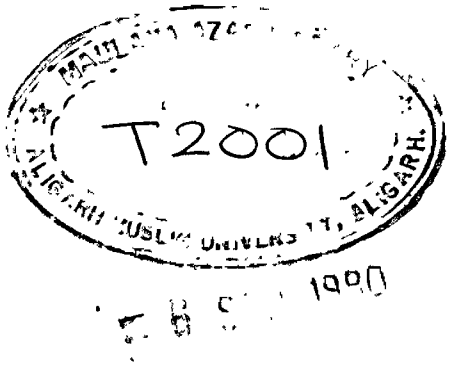
MOHD. ABUZAR GHAFFARI

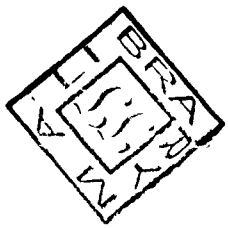
DEPARTMENT OF CHEMISTRY

ALIGARH MUSLIM UNIVERSITY

ALIGARH

1979





ALIGARH MUSLIM UNIVERSITY
ALIGARH, U.P., INDIA

Phone : Office : 3345

Department of Chemistry

STEROID RESEARCH LABORATORY

Date

This is to certify that the work described in this thesis is the original work of the candidate done under my supervision. The thesis is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

Shafiullah

(Dr. Shafiullah)
Lecturer in Chemistry

ACKNOWLEDGEMENTS

I am extremely grateful to Prof. M.S. Ahmad for useful discussion, Prof. W. Rahman, Head, Department of Chemistry, for providing necessary facilities and to CSIR (New Delhi) for financial assistance.

(Mohd. Abuzar Ghaffari)

C O N T E N T S

SUMMARY

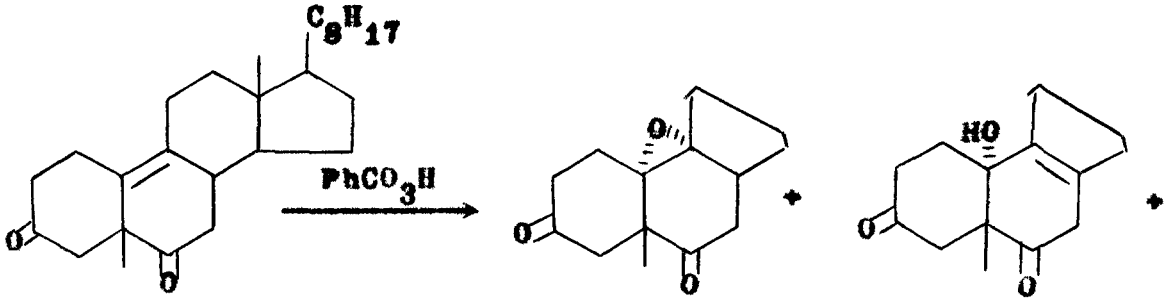
Part - I

Baeyer-Villiger oxidation of steroidal ketones

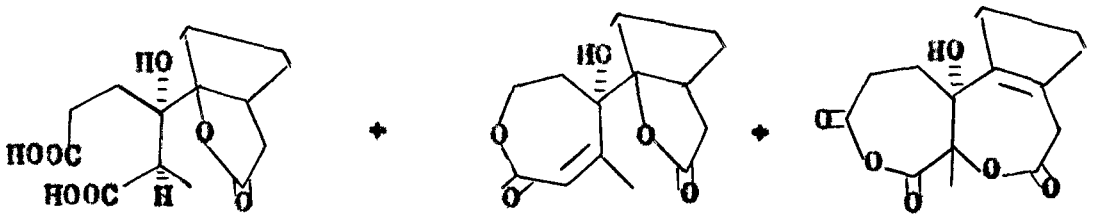
The synthetic modification of steroids has been a major chemical endeavor in the past several decades. A number of papers on preparation of steroidal lactones, seco acids and rearranged products have appeared in literature. Some of the derivatives of 5,6-secosteroids have been shown to possess cytotoxic behaviour and are thus of possible interest as antitumor agents. In the present investigation, we subjected unexplored and easily accessible ketones such as, 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (I), 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (II), 4,4-dimethylcholest-5-en-3-one (III), 4-methylcholest-4-en-3-one (IV) and its ethyl derivatives (V) and (VI) to Baeyer-Villiger oxidation in view to obtain interesting lactones and seco acids. The products obtained were characterized by their chemical and spectral studies.

The ketone (I) under Baeyer-Villiger oxidation condition gave (VII), (VIII) along with abnormal products (IX), (X) and (XI). The subsequent hydrolysis of (XI) provided seco acid (XII). The ketone (II) afforded the compounds (XIII) and (XIV)[a].

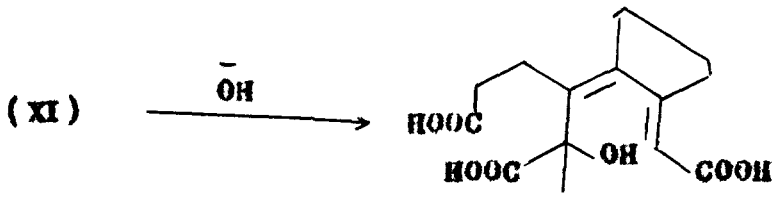
a. Baeyer-Villiger oxidation of C19-norketosteroids Tetrahedron - - - (Communicated).



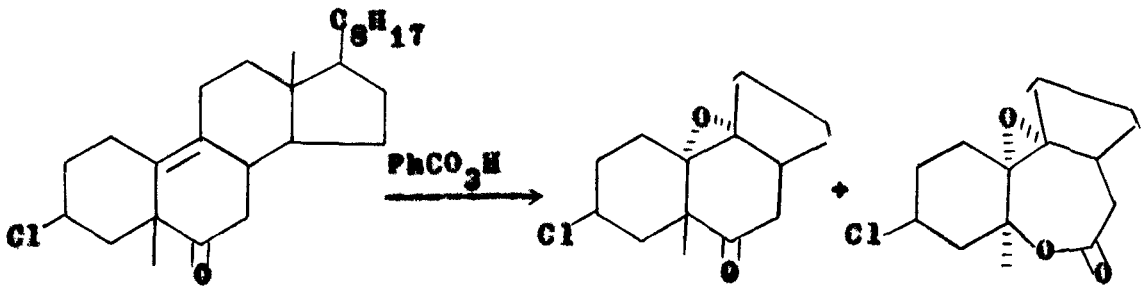
(I) (VII) (VIII)



(IX) (X) (XI)

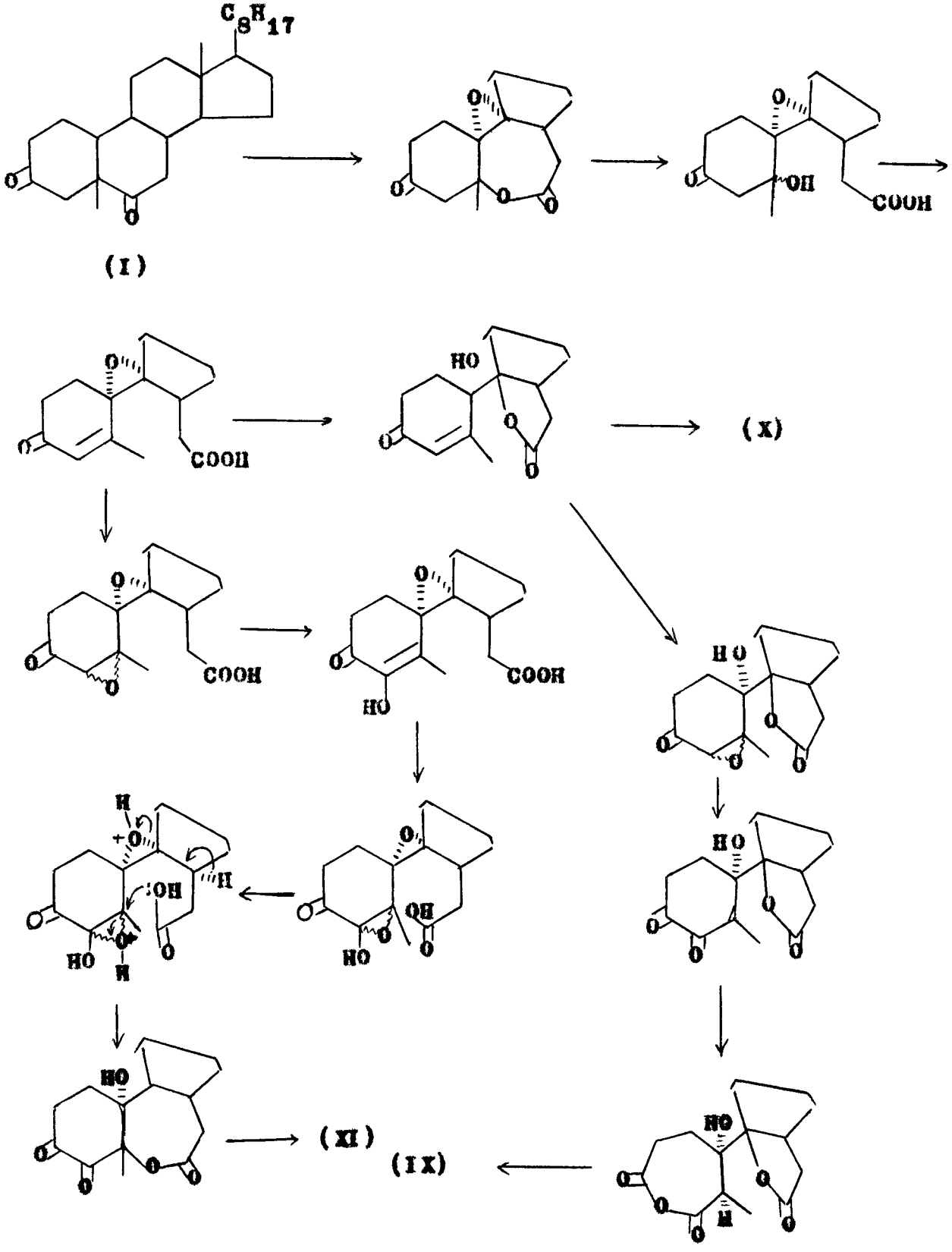


(XII)

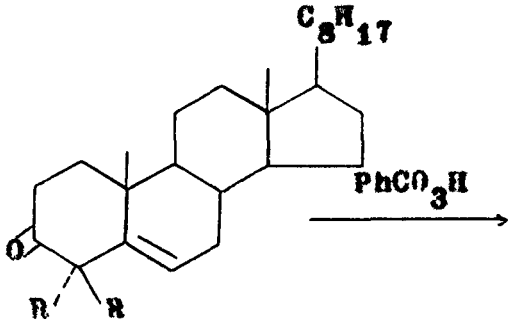


(II) (XIII) (XIV)

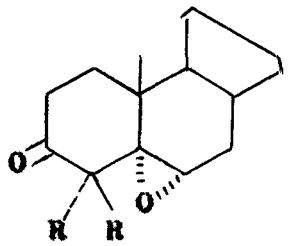
Formation of products (IX), (X) and (XI) can be explained according to the mechanism suggested as follows:



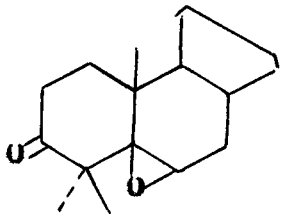
On similar treatment, with perbenzoic acid ketones (III-VI) gave the products[b] which are given below:



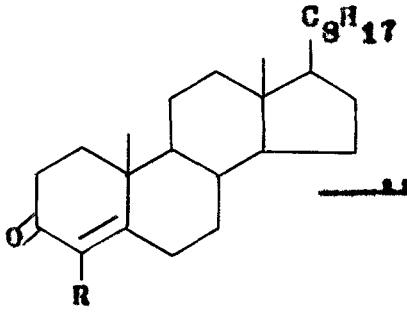
	R
(III)	CH_3
(V)	C_2H_5



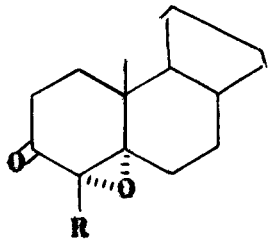
	R
(XV)	CH_3
(XX)	C_2H_5



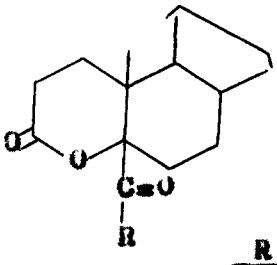
(XVI)



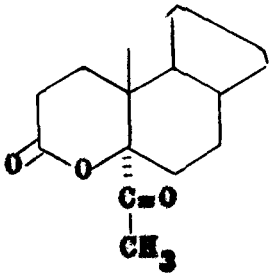
	R
(IV)	CH_3
(VI)	C_2H_5



	R
(XVII)	CH_3
(XXI)	C_2H_5



	R
(XIX)	CH_3
(XXII)	C_2H_5



(XVIII)

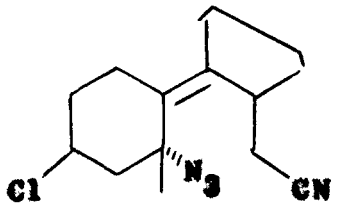
---

b. Baeyer-Villiger oxidation of steroidal ketones J. Ind. Chem. Soc., - - - - (In press).

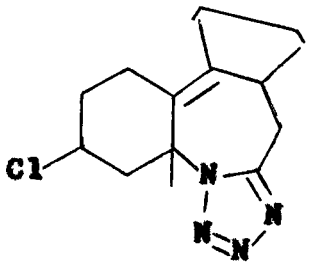
Part - II

Steroidal Tetrazoles

In the recent past, a number of steroidal tetrazoles were synthesized in our laboratory mainly pertaining to ring A and B which may be of potential lipolysis inhibitors. Further attempts were made in present study to synthesize the steroidal tetrazoles derived from hitherto unexplored steroidal ketones such as (II), (III), (IV), (V) and (VI). The ketone (II) on treatment with excess of hydrazoic acid (BF_3-etherate catalyst) gave seco nitrile (XXIII)(abnormal product) and a tetrazole (XXIV)[c]. The ketone (III) on similar treatment gave diketone (XXV) and a tetrazole (XXVI) while (V) furnished seco nitrile (XXVII) and a tetrazole (XXVIII). Under identical reaction conditions, ketone (IV) yielded lactam (XXIX) and tetrazole (XXX) while (VI) gave isomeric tetrazoles (XXXI) and (XXXII)[d].



(XXIII)

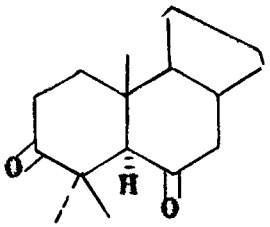


(XXIV)

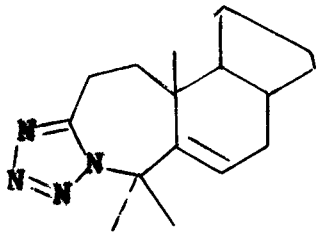
---

c. Schmidt Reaction of 19-nor keto steroid. Approved for presentation during 67th session of the Science Congress, Jan. 1980.

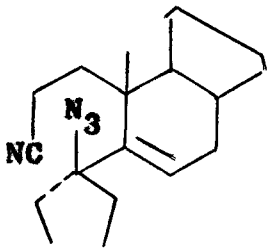
d. Ring A-fused steroidal tetrazoles. Acta. Chim. Acad. Sci. Hungary - - - (In press).



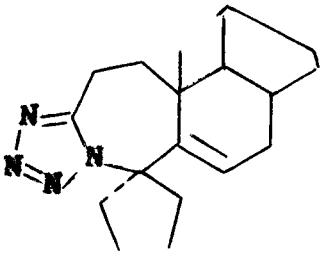
(XXV)



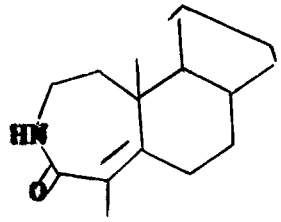
(XXVI)



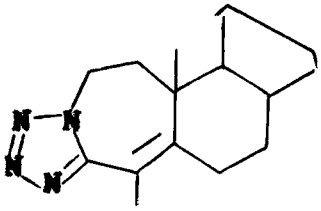
(XXVII)



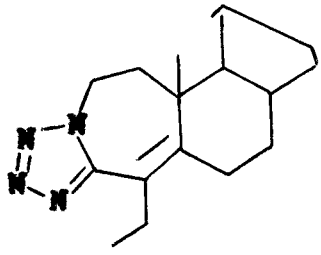
(XXVIII)



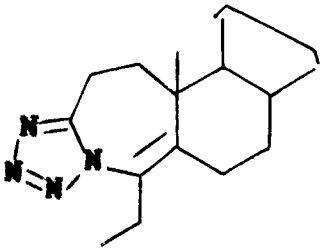
(XXIX)



(XXX)



(XXXI)

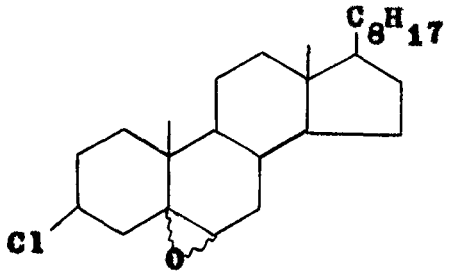


(XXXII)

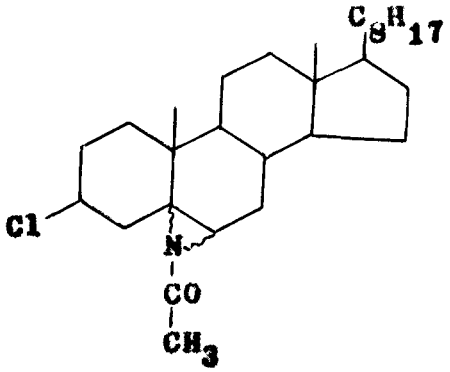
Part - III

Synthesis of Steroidal aziridines

A number of papers appeared on the synthesis of aziridine in recent years and few of them are claimed to possess biological activity. This prompted us to synthesize new steroidal aziridines (XXXVII) and (XXXIX)[e] from 3β-chloro-5,6α-epoxy-5α-cholestane (XXXIII) and its β-isomer (XXXIV) respectively which are worthy of biological testing.



(XXXIII) 5α,6α
(XXXIV) 5β,6β



(XXXVII) 5β,6β
(XXXIX) 5α,6α

---

e. Stereoselective synthesis of steroidal aziridines Synthetic Communications 9(8), 677-682 (1979).

THEORETICAL

The oxasteroids, which contain oxygen atom inserted in the steroid ring structure, with therapeutic properties, stimulated extensive research and this resulted in the preparation of a variety of oxygen heterocyclic compounds with useful biological activity. These oxasteroids were found to be of great importance as synthetic intermediates in many reactions. As intermediates, they became important for the insertion of labelled oxygen into steroid nucleus, ring contraction and preparation of methyl derivatives. Oxasteroids are usually prepared in the form of an ether lactone, anhydride and as derivatives of lactones.

Of various methods used for the insertion of oxygen atom in carbon frame work, the most widely and convincing method is the Baeyer-Villiger oxidation of ketones. This chapter envisages the coverage of literature for the preparation of oxasteroids.

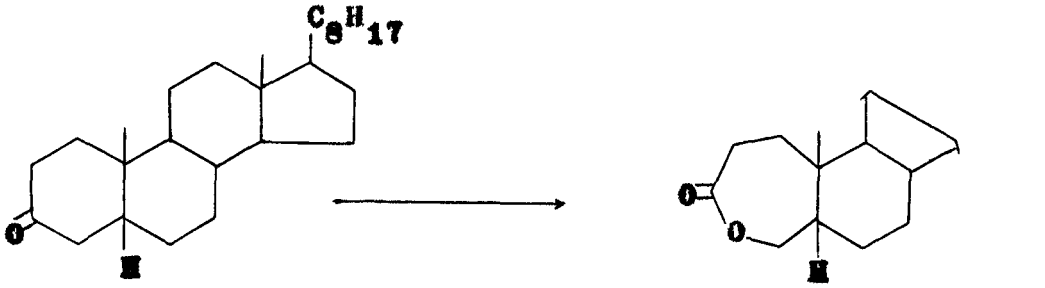
In 1899, Baeyer and Villiger[1] reported the first example of the peracid oxidation of ketones to corresponding esters or lactones. They used Caro's acid, but in subsequent years several other peroxy acids also came into use, of which the principal ones are peracetic, trifluoroperacetic, perbenzoic and monoperphthalic acids. Reaction can also be brought about by hydrogen peroxide in basic medium. Since that time this type of oxidation has found a wide variety of important synthetic and degradative

applications. An excellent review on the subject is given by Hassall[2]. Thus peracids have been used to synthesise a variety of steroid and terpene lactones as well as lactones involving medium and large ring which are virtually difficult to obtain by other means.

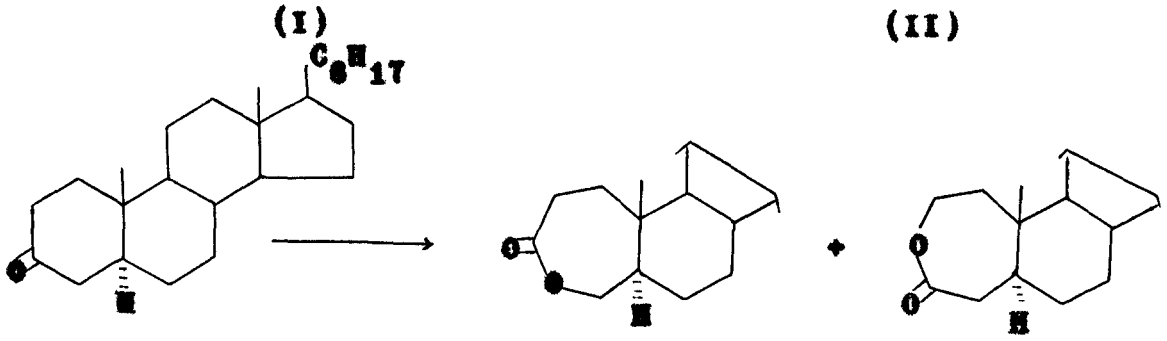
Baeyer-Villiger Oxidation of steroidal ketones

A. Saturated Ketones

It has been reported by Gardner and Godden[3] that 5β-cholestan-3-one (I) on heating with ammonium persulphate and aqueous acetic acid afforded a single lactone, 4-oxa-A-homo-5β-cholestan-3-one (II). But under similar reaction conditions, Ellis and Gardner[4] have shown the formation of two isomeric lactones, 4-oxa-A-homo-5α-cholestan-3-one (IV) and 3-oxa-A-homo-5α-cholestan-4-one (V) from 5α-cholestan-3-one (III).

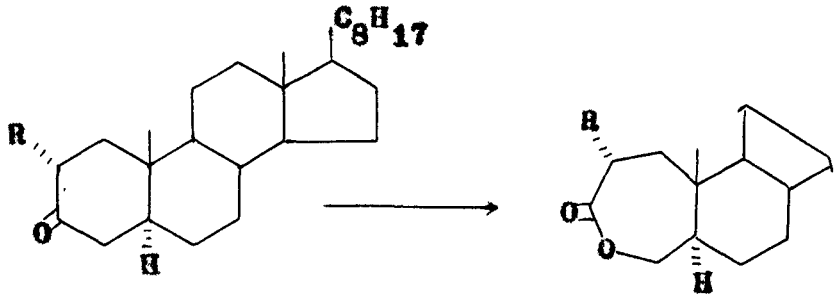


(I) (II)



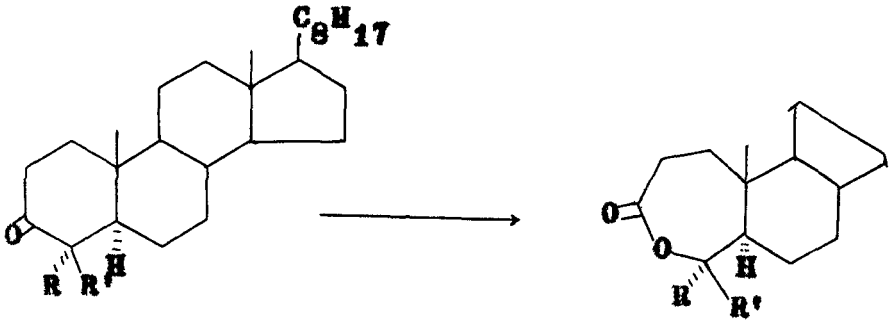
(III) (IV) (V)

Bolliger and Courtney[5] reported the reaction of 2α-halo-5α-cholestan-3-ones (VI-a) and (VI-b) with trifluoroperoxy-acetic acid in chloroform and obtained the corresponding 2α-halo-4-oxa-A-homo-5α-cholestan-3-ones (VII-a) and (VII-b). The formation of 4-oxa isomer in preference to 3-oxa isomer suggested the greater migratory aptitude of C4 in comparison to C2 due to the presence of α-halogen at C2.



	R		R
(VI-a)	Cl	(VII-a)	Cl
(VI-b)	Br	(VII-b)	Br

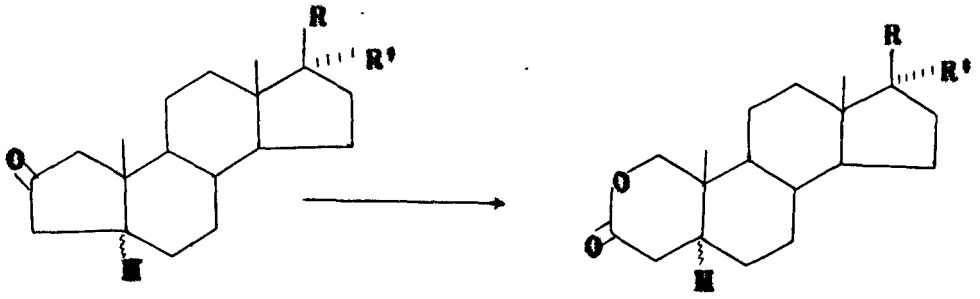
Rosenthal et al.[6] reported the Baeyer-Villiger oxidation of 4α-methyl-5α-cholestan-3-one (VIII), its 4β-methyl analogue (IX) and 4,4-dimethyl-5α-cholestan-3-one (X) with m-chloroperbenzoic acid. The reaction furnished ∈-lactones, 4aα-methyl-4-oxa-A-homo-5α-cholestan-3-one (XI), its 4aβ-analogue (XII) and 4aα, 4aβ-dimethyl-4-oxa-A-homo-5α-cholestan-3-one (XIII). The result showed the preferential migration of a more substituted carbon.



	R	R'
(VIII)	Me	H
(IX)	H	Me
(X)	Me	Me

	R	R'
(XI)	Me	H
(XII)	H	Me
(XIII)	Me	Me

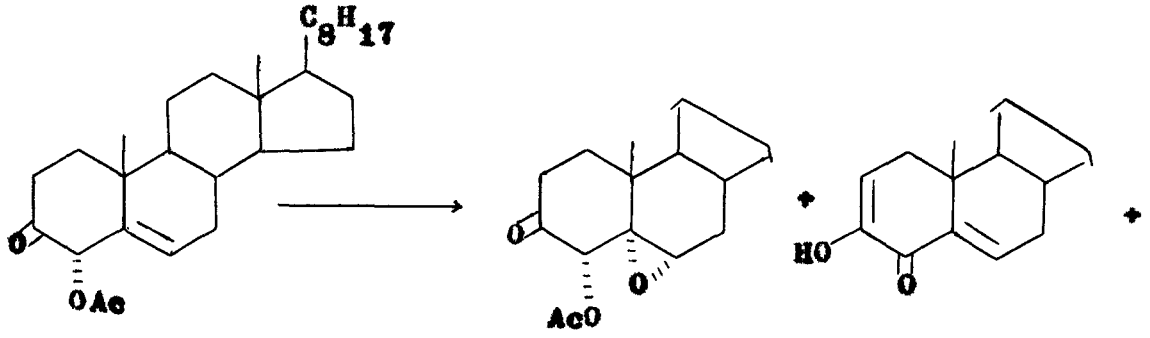
It has been shown by Hara[7] that the Baeyer-Villiger oxidation of 5α- and 5β-2-keto-A-nor-steroids (XIVa-e) under usual reaction conditions afforded exclusively 2-oxasteroids (XVa-e). Interestingly, no 3-oxa-isomers were obtained.



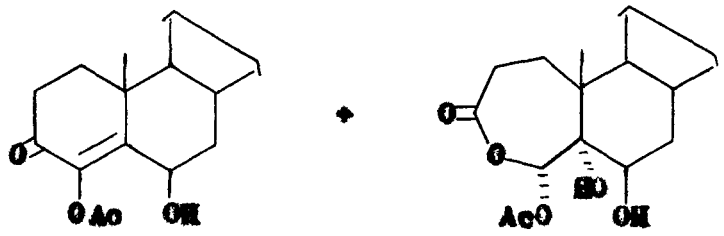
	R	R'
(XIV)-a	C_8H_{17}	H
-b	H	H
-c	OH	H
-d	OAc	H
-e	OH	CH_3

	R	R'
(XV)-a	C_8H_{17}	H
-b	H	H
-c	OH	H
-d	OAc	H
-e	OH	CH_3

Ahmad et al.[8] have reported the oxidation of 4α-acetoxy-cholest-5-en-3-one (XVI) with different concentrations of perbenzoic acid, using p-toluenesulphonic acid monohydrate as the catalyst. The reaction of (XVI) with 1 mole equivalent of perbenzoic acid gave 5,6α-epoxy-4α-acetoxy-5α-cholestan-3-one (XVII), 3-hydroxycholesta-2,5-dien-4-one (XVIII) and 6β-hydroxy-4-acetoxycholest-4-en-3-one (XIX). The ketone (XVI) with an excess of perbenzoic acid (2.5 mole equivalent) yielded only a single product, 5,6β-dihydroxy-4aα-acetoxy-4-oxa-A-homo-5α-cholestan-3-one (XX).

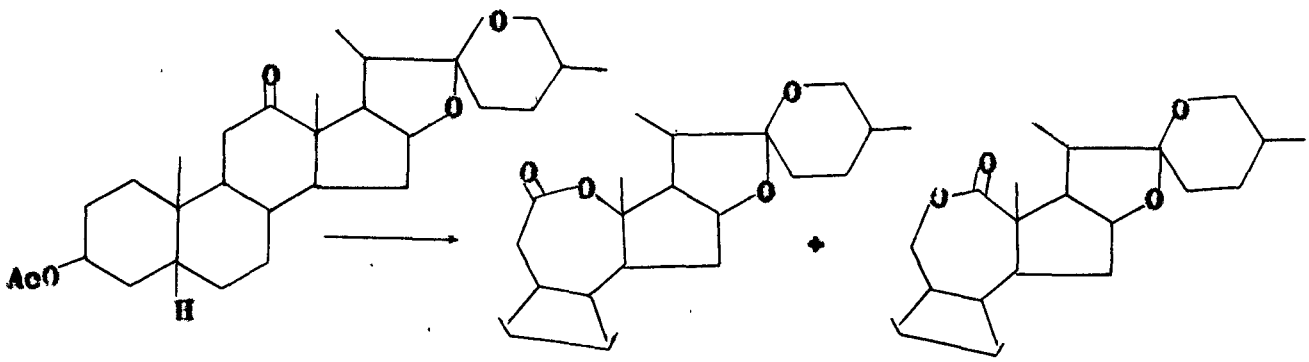


(XVI) (XVII) (XVIII)



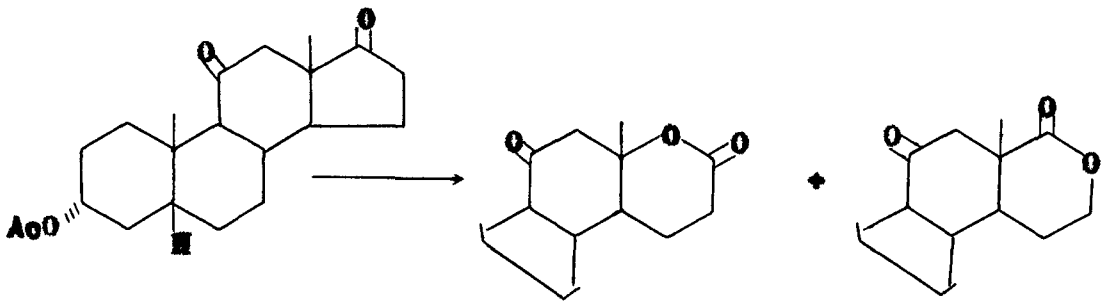
(XIX) (XX)

The Baeyer-Villiger oxidation of hecogenin acetate (XXI) with peracetic and perbenzoic acids by Bladon and McMeakin[9] led to the formation of two isomeric lactones (XXII) and (XXIII).



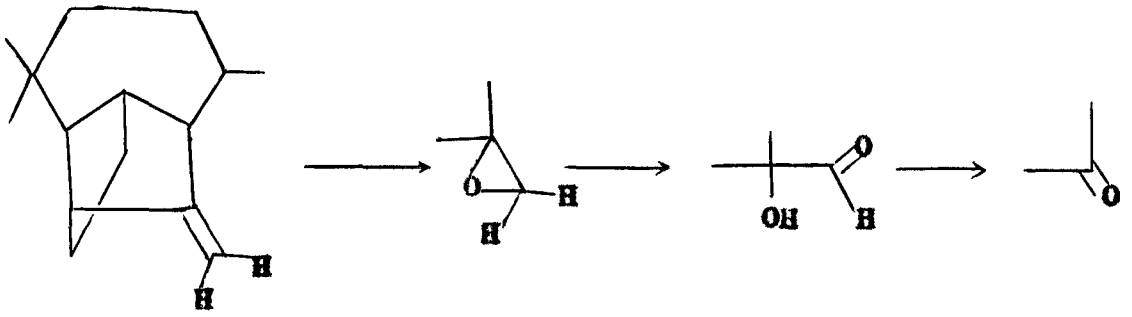
(XXI) (XXII) (XXIII)

It has been reported by Lardon et al.[10] that the perbenzoic acid oxidation of 3α-acetoxy-5β-androstane-11,17-dione (XXIV) furnished two isomeric lactones (XXV) and (XXVI).

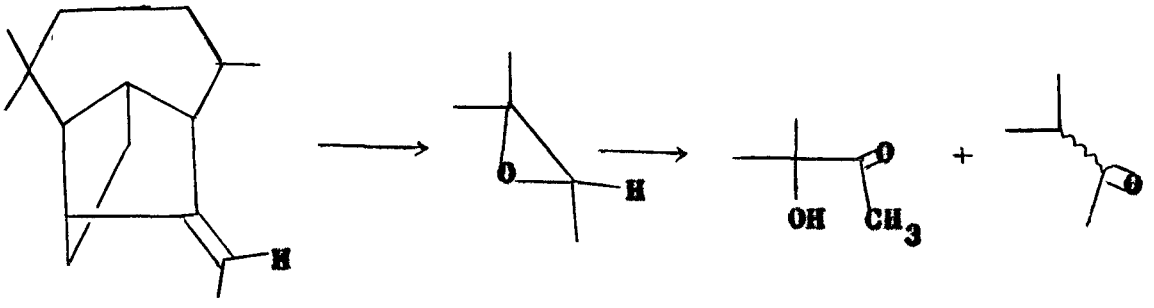


(XXIV) (XXV) (XXVI)

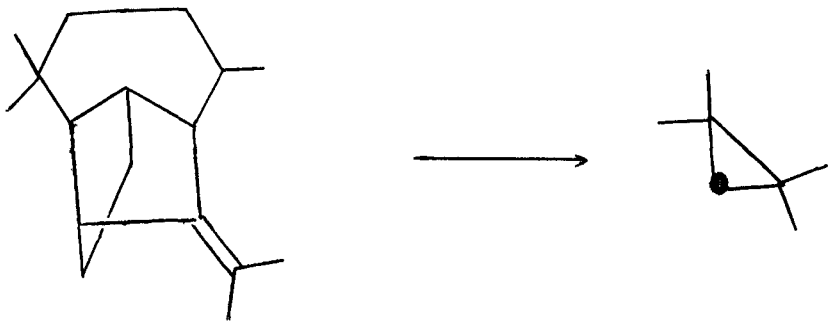
Shivaji et al.[11] treated longifolene (XXVII) with perbenzoic acid under different concentrations and obtained 7,15-epoxylongifolene (XXVIII), hydroxy ketone (XXIX) and ketone (XXX). Similarly ω -methyllongifolene (XXXI) provided 7,15-epoxy-15-methyllongifolane (XXXII), hydroxy methyl ketone (XXXIII) and methyl ketone (XXXIV). ω , ω-dimethyllongifolene (XXXV) yielded 7,15-epoxy-15,15-dimethyllongifolane (XXXVI) only.



(XXVII) (XXVIII) (XXIX) (XXX)

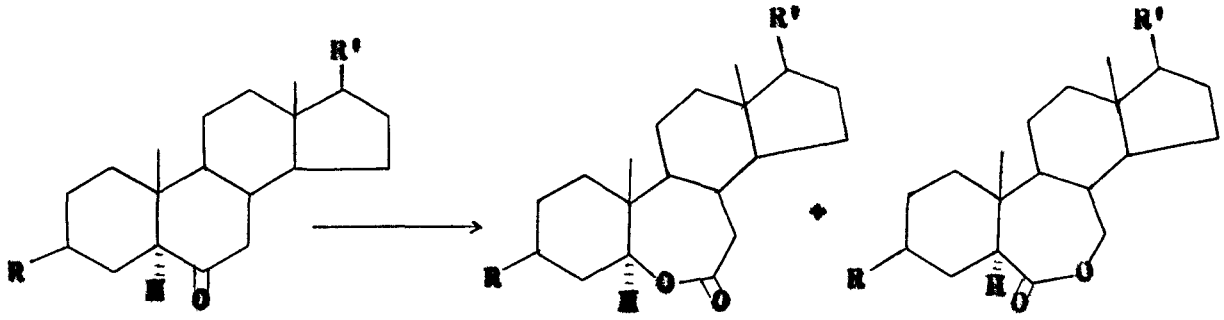


(XXXI) (XXXII) (XXXIII) (XXXIV)



(XXXV) (XXXVI)

Recently, Ahmad et al.[12] subjected 6-keto-5α-β-sitosanyl acetate (XXXVII) to Baeyer-Villiger oxidation using perbensoic acid (1 mole equivalent) as oxidant and obtained expected 6-oxalactone (XXXVIII) as well as the isomeric 7-oxalactone (XXXIX) which was totally unexpected in view of the conclusion arrived at previously[13,14] that Baeyer-Villiger oxidation of 6-keto-steroids is a stereospecific process leading to entirely the 6-oxasteroids by superior migration of a more substituted C5 relative to C7. This led them to scrutinate the peracid oxidation of (XLIII), (XLVI), (XLIX) and 3β-hydroxy-5α-cholestan-6-one (XL). In each case they obtained the isomeric lactones and concluded afresh that C7, though less substituted than C5, competes effectively for migration to an electron deficient oxygen.

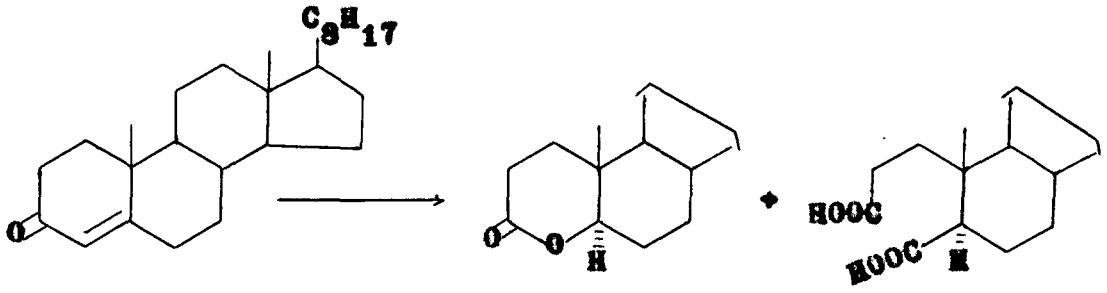


	R	R'		R	R'		R	R'
(XXXVII)	OAc	$C_{10}H_{21}$	(XXXVIII)	OAc	$C_{10}H_{21}$	(XXXIX)	OAc	$C_{10}H_{21}$
(XL)	OH	C_8H_{17}	(XLI)	OH	C_8H_{17}	(XLII)	OH	C_8H_{17}
(XLIII)	H	C_8H_{17}	(XLIV)	H	C_8H_{17}	(XLV)	H	C_8H_{17}
(XLVI)	OAc	C_8H_{17}	(XLVII)	OAc	C_8H_{17}	(XLVIII)	OAc	C_8H_{17}
(XLIX)	Cl	C_8H_{17}	(L)	Cl	C_8H_{17}	(LI)	Cl	C_8H_{17}

B. α,β-Unsaturated Ketones

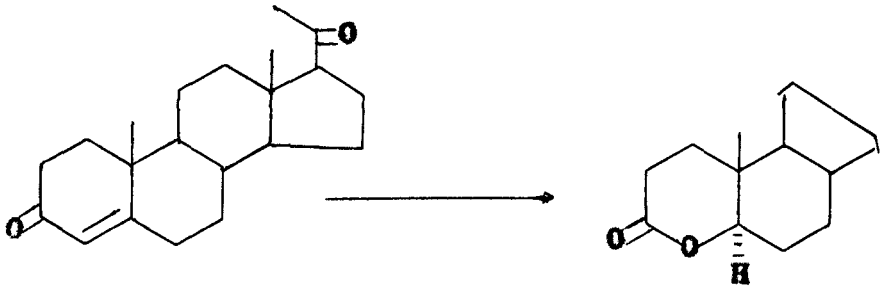
Structural elements other than carbonyl group may be attacked under the conditions used for the Baeyer-Villiger oxidation. The susceptibility of olefin linkage to oxidation by peracids is well known. α,β-Unsaturated ketones on peracid oxidation may lead to the formation of enol esters, epoxy ketones and epoxyesters[15-18]. However, depending on the reaction conditions and peracid used, Δ^4-3-ketosteroids may yield large variety of products. Thus perbenzoic acid oxidation containing perchloric acid as the catalyst has been reported to afford a mixture of enol lactones and epoxy lactones[19] but potassium persulphate and sulphuric acid provided 3-keto-4-oxasteroids[20-22].

In 1941, Salamon[20] and later Turner[21] performed the Baeyer-Villiger oxidation of cholest-4-en-3-one (LII) with potassium persulphate and sulphuric acid and reported the formation of 4-oxa-5α-cholestan-3-one (LIII) and the acid (LIV).

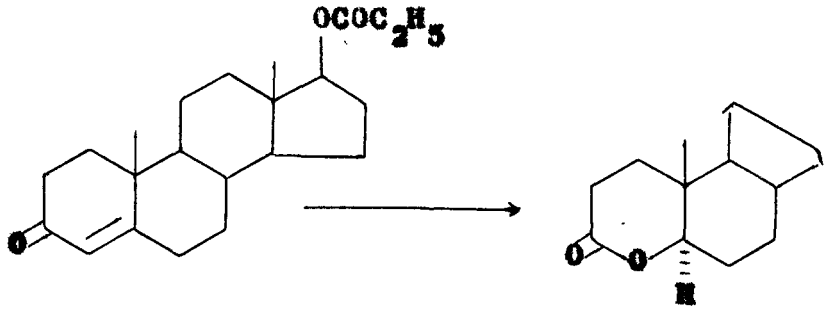


(LII) (LIII) (LIV)

It has been reported by Petit and Kasturi[22] that the peroxy sulphuric acid oxidation of progesterone (LV) and testosterone propionate (LVI) yielded the 4-oxa-3-keto-5α-steroids (LVII) and (LVIII) respectively.

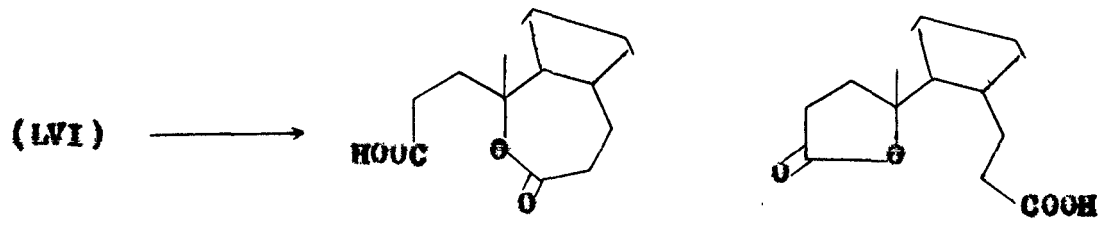


(LV) (LVII)



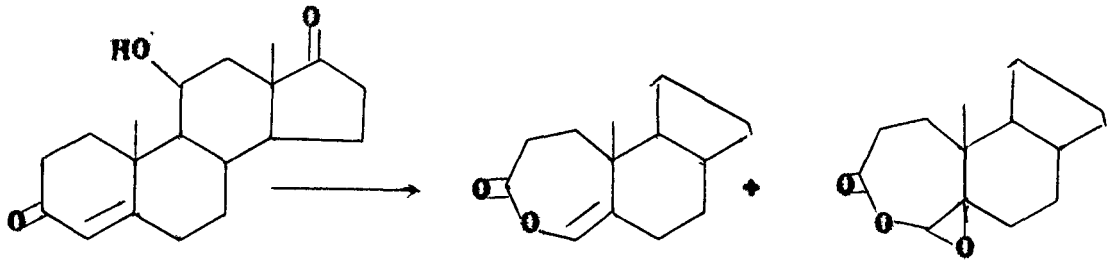
(LVI) (LVIII)

Testosterone propionate (LVI) on treatment with hydrogen peroxide in the presence of Selenium dioxide in t-butyl alcohol, afforded ϵ-lactone carboxylic acid (LIX) and the γ-lactone acid (LX)[23].



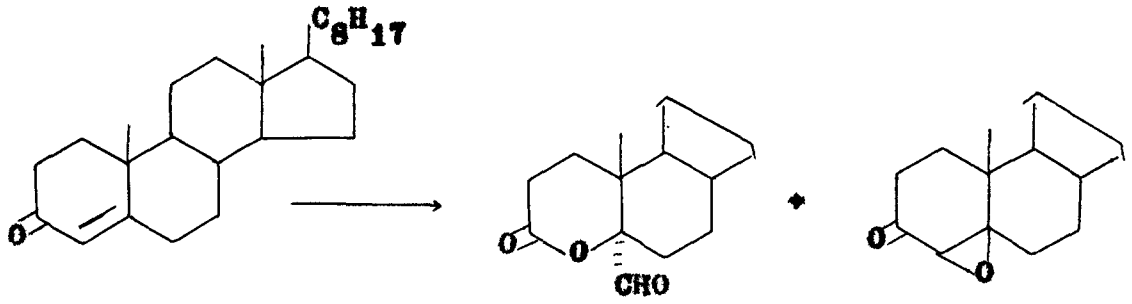
(LIX) (LX)

Caspi et al.[19] carried out the Baeyer-Villiger oxidation of 11β-hydroxyandrost-4-ene-3,17-dione (LXI) which furnished 11β-hydroxy-4-oxa-A-homoandrost-4a-ene-3,17-dione (LXII) along with small quantity of 11β-hydroxy-4-oxa-4aβ,5-epoxy-A-homo-5β-androstane-3,17-dione (LXIII).



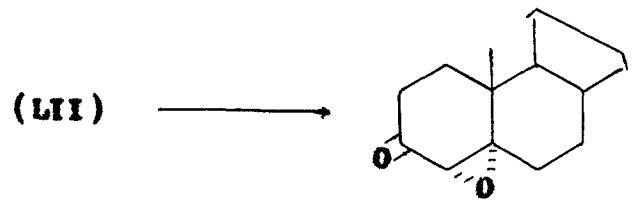
(LXI) (LXII) (LXIII)

Pinhey and Schaffner[24] performed the Baeyer-Villiger oxidation of cholest-4-en-3-one (LII) with trifluoroperacetic acid in buffer solution and reported the formation of 5-formyl-4-oxa-5α-cholestan-3-one (LXIV) and 4β,5-epoxy-5β-cholestan-3-one (LXV).

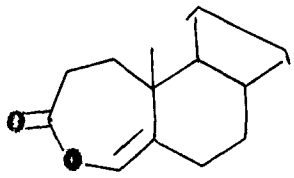


(LII) (LXIV) (LXV)

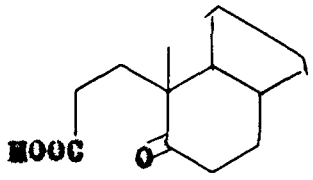
Pinhey and Schaffner[25] carried out the Baeyer-Villiger oxidation of (LII) with perbenzoic acid in the presence of anhydrous perchloric acid and obtained 4α,5-epoxy-5α-cholestan-3-one (LXVI), 4-oxa-A-homocholest-4a-en-3-one (LXVII), (LXIV) and 3,5-seco-4-norcholest-5-one-3-oic acid (LXVIII).



(LXVI)



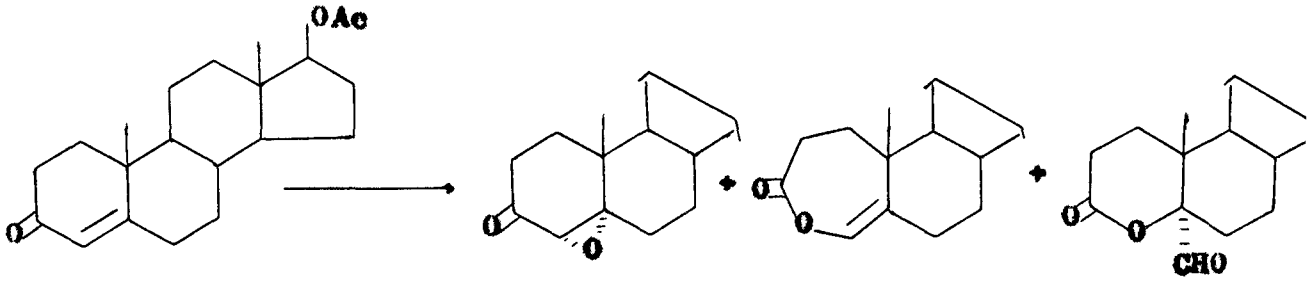
(LXVII)



(LXVIII)

A detailed study of the oxidation of testosterone acetate (LXIX) with perbenzoic acid and m-chloroperbenzoic acid in the presence of anhydrous perchloric acid as the catalyst has been done by Mazur et al.[26] They corelated the formation of the products with the quantity of peracid used, its concentration and reaction period.

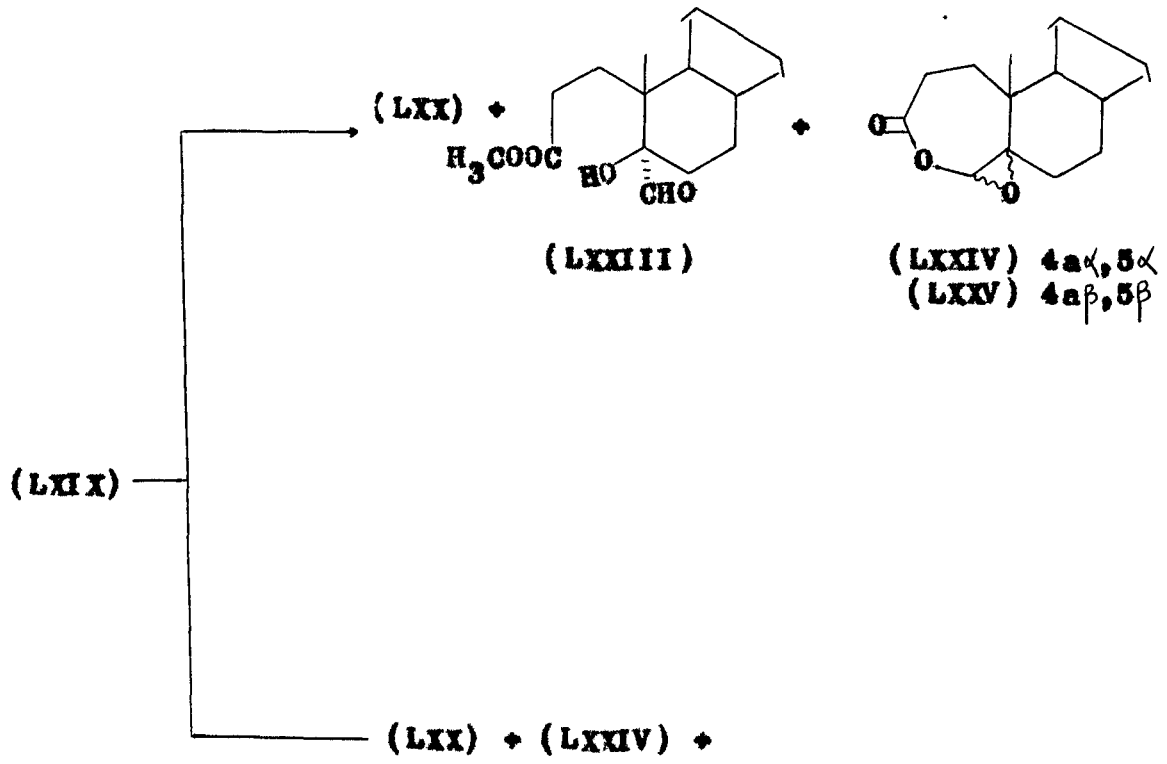
The oxidation of (LXIX) with perbenzoic acid (1 mole equivalent) in the presence of anhydrous perchloric acid for 12 hrs afforded, 17β-acetoxy-4α,5-epoxy-5α-androstan-3-one (LXX), 17β-acetoxy-5-formyl-4-oxa-5α-androstan-3-one (LXXI) and 17β-acetoxy-4-oxa-4-homoandrost-4a-en-3-one (LXXII).

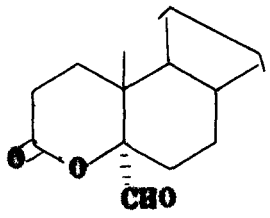


(LXIX) (LXX) (LXXII) (LXXI)

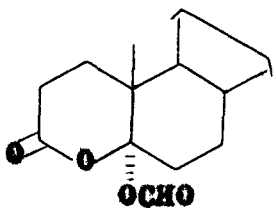
The ketone (LXIX) on treatment with perbenzoic acid (2 mole equivalent) in the presence of anhydrous perchloric acid as catalyst for 84 hrs furnished (LXX), methyl-17β-acetoxy-3,5-seco-4-nor-5β-hydroxy-5β-formylandrostan-3-oate (LXXIII) and 17β-acetoxy-4a,5-epoxy-4-oxa-A-homo-5α-androstan-3-ones (LXXIV

and LXXV). When (LXIX) was treated with an excess of perbenzoic acid (4 mole equivalent) (LXX), (LXXIV), 5-formyl-δ-lactones (LXXI and LXXVI) and 17β-acetoxy-5-formate-4-oxa-5α-androstan-3-one (LXXVII) were obtained.



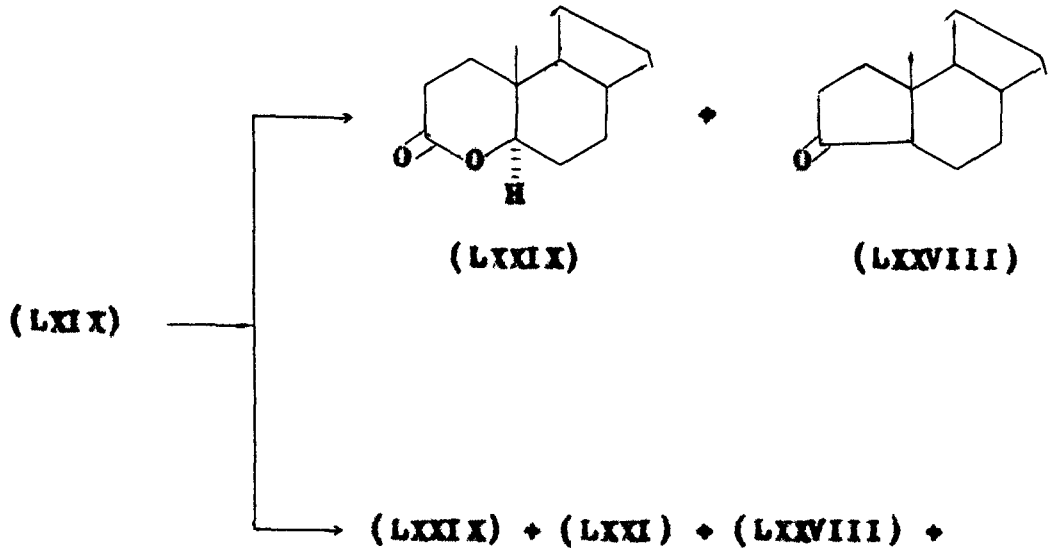


(LXXI) 5α-
(LXXVI) 5β-

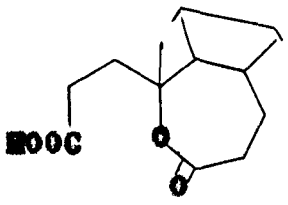


(LXXVII)

When the reaction was performed with perbenzoic acid (2 mole equivalent) in the presence of aqueous perchloric acid for 12 hrs, 17β-acetoxy-A-norandrostan-3-one (LXXVIII) and the δ-lactone (LXXIX) were obtained from (LXIX). Similarly when m-chloroperbenzoic acid was used as oxidant and aqueous perchloric acid as the activator, (LXIX) afforded (LXXIX), (LXXI), 17β-acetoxy-3,5-seco-4-nor-5-oxa-B-homoandrostan-6-one-2-carboxylic acid (LXXX) and A-norketone (LXXVIII) after a period of 12 hrs.

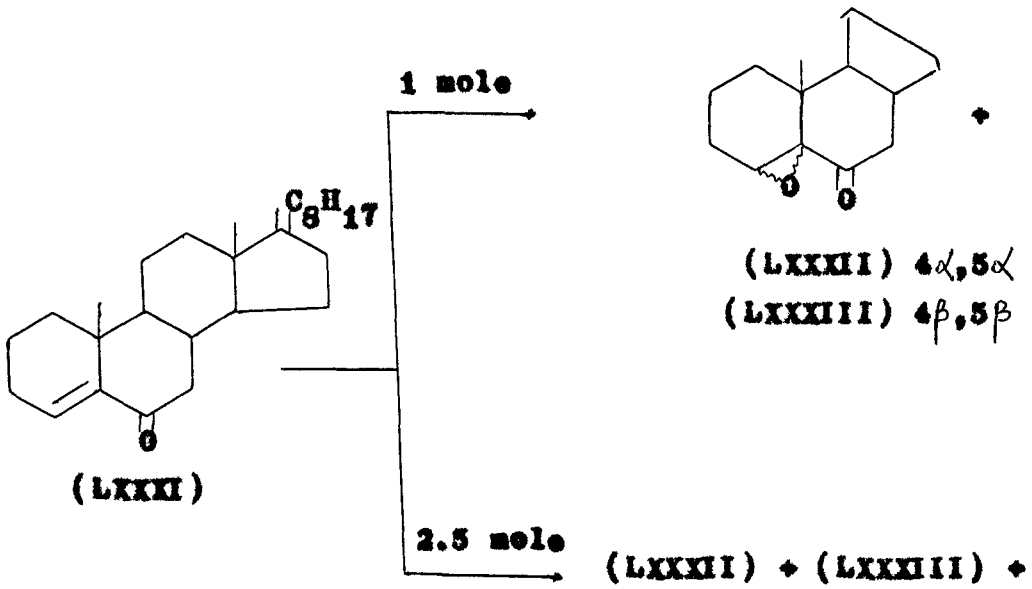


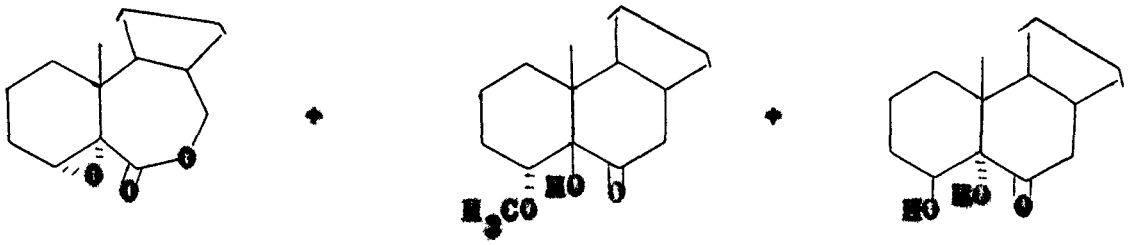
(LXXIX) + (LXXVIII)



(LXXX)

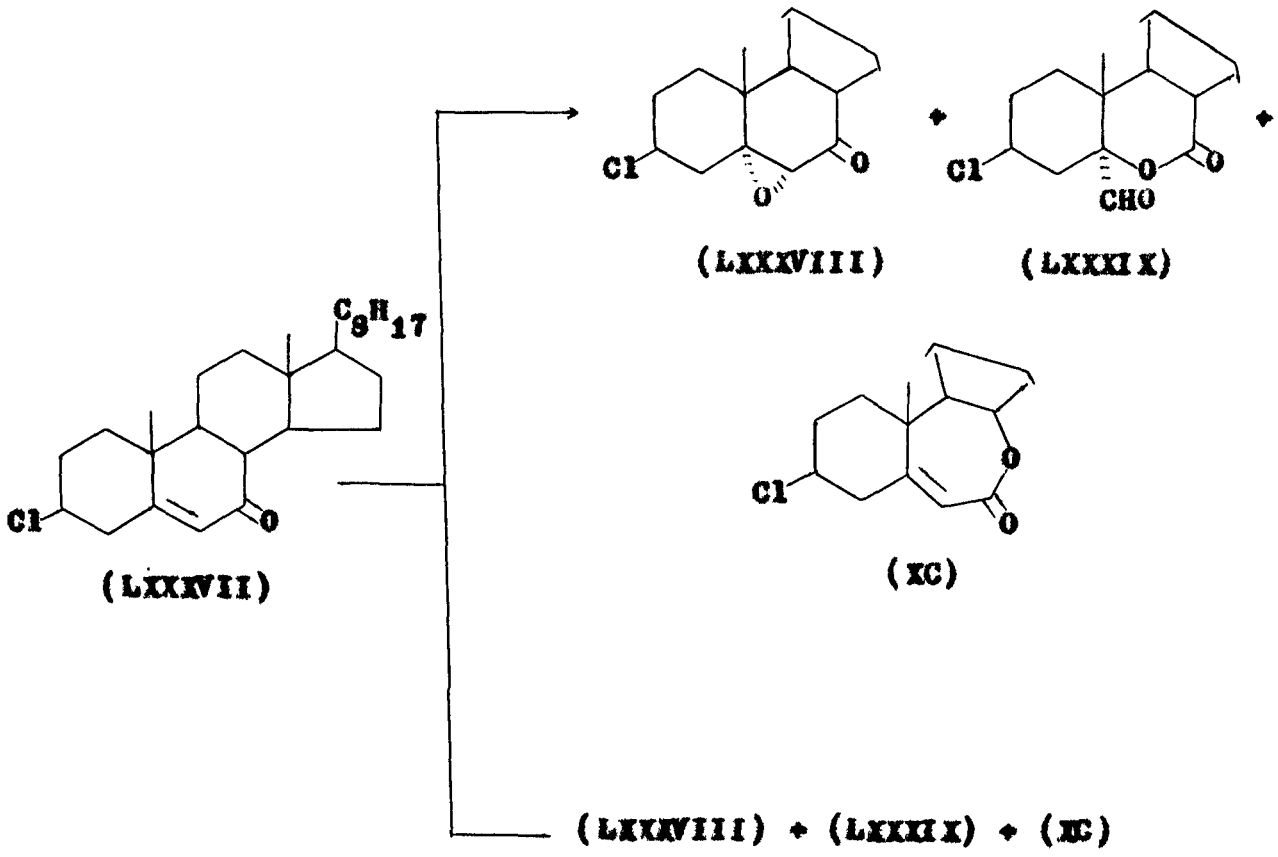
Ahmad et al.[27] have reported the Baeyer-Villiger oxidation of cholest-4-en-6-one (LXXXI). Treatment of (LXXXI) with perbenzoic acid (1 mole equivalent) using p-toluenesulphonic acid monohydrate as catalyst gave 4α,5-epoxy-5α-cholestan-6-one (LXXXII) and 4β,5-epoxy-5β-cholestan-6-one (LXXXIII). When (LXXXI) was treated with an excess of perbenzoic acid (2.5 mole equivalent)(LXXXII), (LXXXIII), 4α,5-epoxy-7-oxa-B-homo-5α-cholestan-6-one (LXXXIV), 5-hydroxy-4α-methoxy-5β-cholestan-6-one (LXXXV) and 4β,5-dihydroxy-5α-cholestan-6-one (LXXXVI) were obtained.

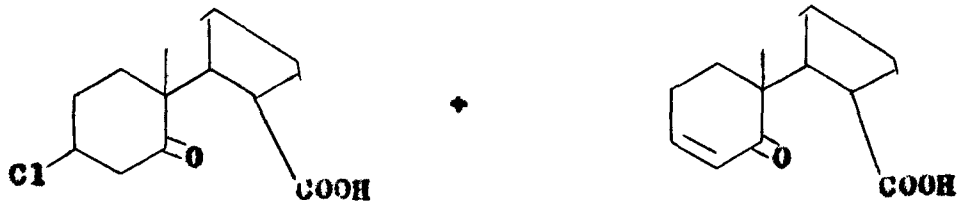




(LXXXIV) (LXXXV) (LXXXVI)

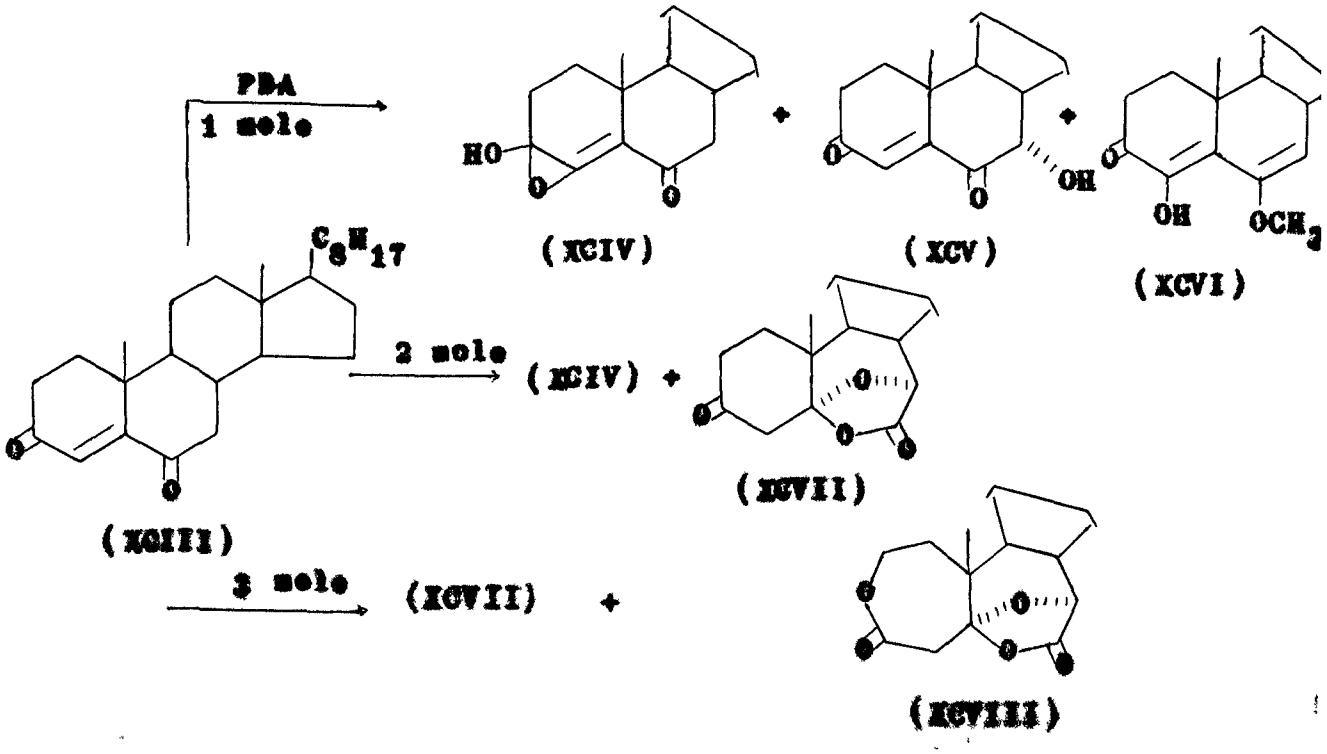
Recently Shafiullah et al.[28] oxidised 3β-chlorocholest-5-en-7-one (LXXXVII) with different concentrations of perbenzoic acid and obtained a variety of products. Oxidation of (LXXXVII) with perbenzoic acid (1 mole equivalent) using p-toluenesulphonic acid monohydrate as catalyst gave 3β-chloro-5,6α-epoxy-5α-cholestan-7-one (LXXXVIII), 3β-chloro-5-formyl-6-oxa-5α-cholestan-7-one (LXXXIX) and 3β-chloro-7a-oxa-B-homocholest-5-en-7-one (XC). When treated with an excess of perbenzoic acid (2.5 mole equivalent), (LXXXVII) provided (LXXXVIII), (LXXXIX), (XC), 3β-chloro-5-oxa-5,7-seco-6-norcholestan-7-oic acid (XCI) and 5-oxa-5,7-seco-6-norcholestan-3-en-7-oic acid (XCII).





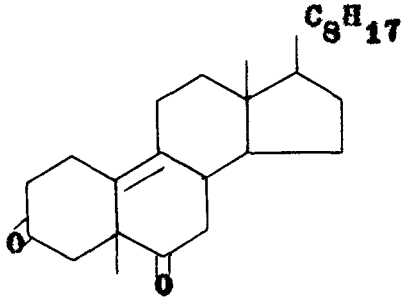
(XCI) (XCII)

Ahmad et al.[29] carried out the Baeyer-Villiger oxidation of cholest-4-ene-3,6-dione (XCIII) which gave very interesting results. With 1 mole equivalent of perbenzoic acid, (XCIII) gave 3-hydroxy-3,4-oxidocholest-4-en-6-one (XCIV), 7α-hydroxy-cholest-4-ene-3,6-dione (XCV) and 4-hydroxy-6-methoxycholesta-4,6-dien-3-one (XCVI). With 2 mole equivalent of perbenzoic acid, (XCIII) afforded (XCIV) and a novel oxetalactone, 5,7aα-oxido-6-oxa-A-homo-5α-cholestane-3,7-dione (XCVII). With 3 mole equivalent of perbenzoic acid, (XCIII) furnished (XCVII) and its product of further oxidation, 5,7aα-oxido-3,6-dioxa-A,B-bishomo-5α-cholestane-4,7-dione (XCVIII).

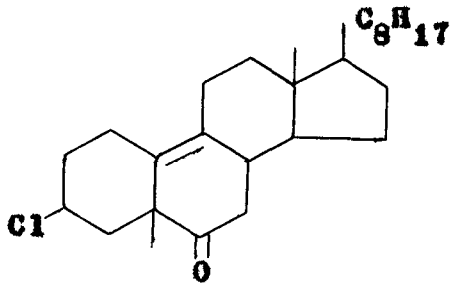


DIECUSSION

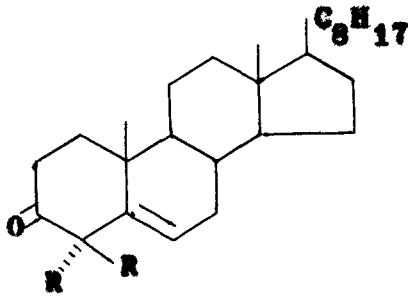
Several papers dealing with the preparation of oxasteroids have appeared from these laboratories. The present work is employed on hitherto unexplored steroidal ketones, such as 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (XCIX), 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (C), 4,4-dimethylcholest-5-en-3-one (CI), 4-methylcholest-4-en-3-one (CIII) and ethyl analogues of (CI) and (CIII), i.e. (CII)(CIV).



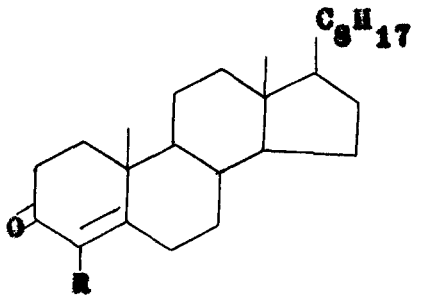
(XCIX)



(C)



	R
(CI)	CH_3
(CIII)	C_2H_5



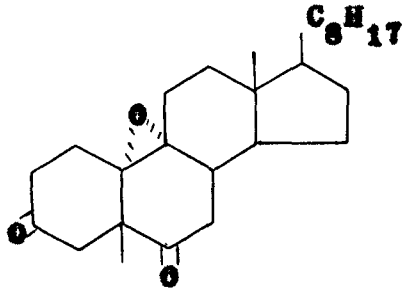
	R
(CII)	CH_3
(CIV)	C_2H_5

Baeyer-Villiger Oxidation of 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (XCIX)

The diketone (XCIX) was treated with perbenzoic acid (2.5 mole equivalent) in chloroform in the presence of p-toluenesulphonic acid as catalyst. The reaction mixture was allowed to stand at room temperature for 4 days. The reaction mixture after usual work up and column chromatography over silica gel provided compounds, m.p. 132°, 175°, 178°, 170° and a non-crystallizable oil.

Characterization of the compound, m.p. 132° as 5-methyl-19-nor-9α,10α-epoxy-5β-cholestane-3,6-dione (CV)

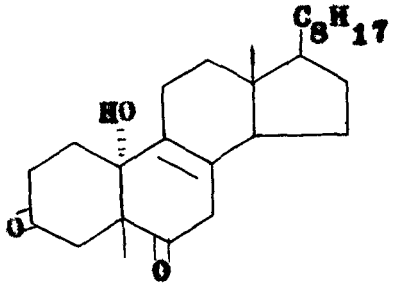
The compound (CV), m.p. 132° was analysed for $C_{27}H_{42}O_3$. The molecular composition indicated the addition of an oxygen atom to the substrate (XCIX). The m.p., t.l.c. and IR values were found identical to the authentic sample (reported[30] m.p. 132°).



(CV)

Characterization of the compound, m.p. 175° as 5-methyl-10α-hydroxy-19-nor-5β-cholest-8(9)-ene-3,6-dione (CVI)

The compound, m.p. 175° was analysed for $C_{27}H_{42}O_3$ ($M^{+\cdot}$ 414) (positive tetranitromethane test). The molecular composition indicated the addition of an oxygen atom to the substrate (XCIX). A sharp band at 3400 cm^{-1} in IR spectrum of the compound signified the presence of tertiary OH. The strong bands at 1725 and 1700 cm^{-1} were ascribed to two carbonyl groups. From the elemental analysis and IR data, it is concluded that the carbonyl functions are unaltered. The NMR spectrum of the compound was found to be featureless in the downfield region. A multiplet centred at δ 2.55 was assigned to α-keto methylene protons (C2-$\underline{H}_2$, C4-$\underline{H}_2$, C7-$\underline{H}_2$). Other signals were observed at δ 1.05 (C5-$C\underline{H}_3$), 0.7 (C13-$C\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons).



(CVI)

The structure (CVI) was further supported by mass spectral study. The (CVI)(Fig. 1) showed the molecular ion peak at m/e 414 ($C_{27}H_{42}O_3$; base peak). The other diagnostic peaks were at

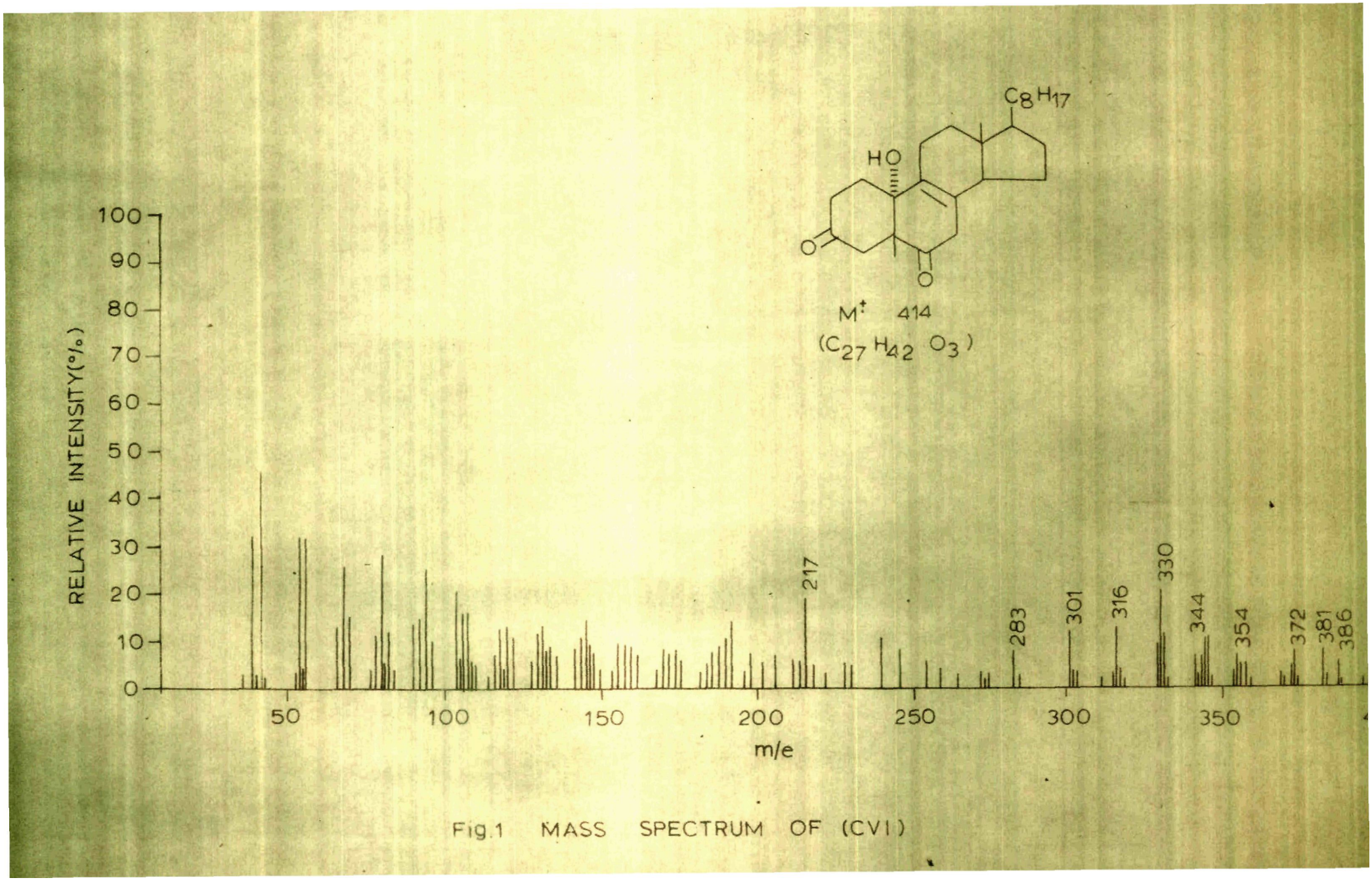
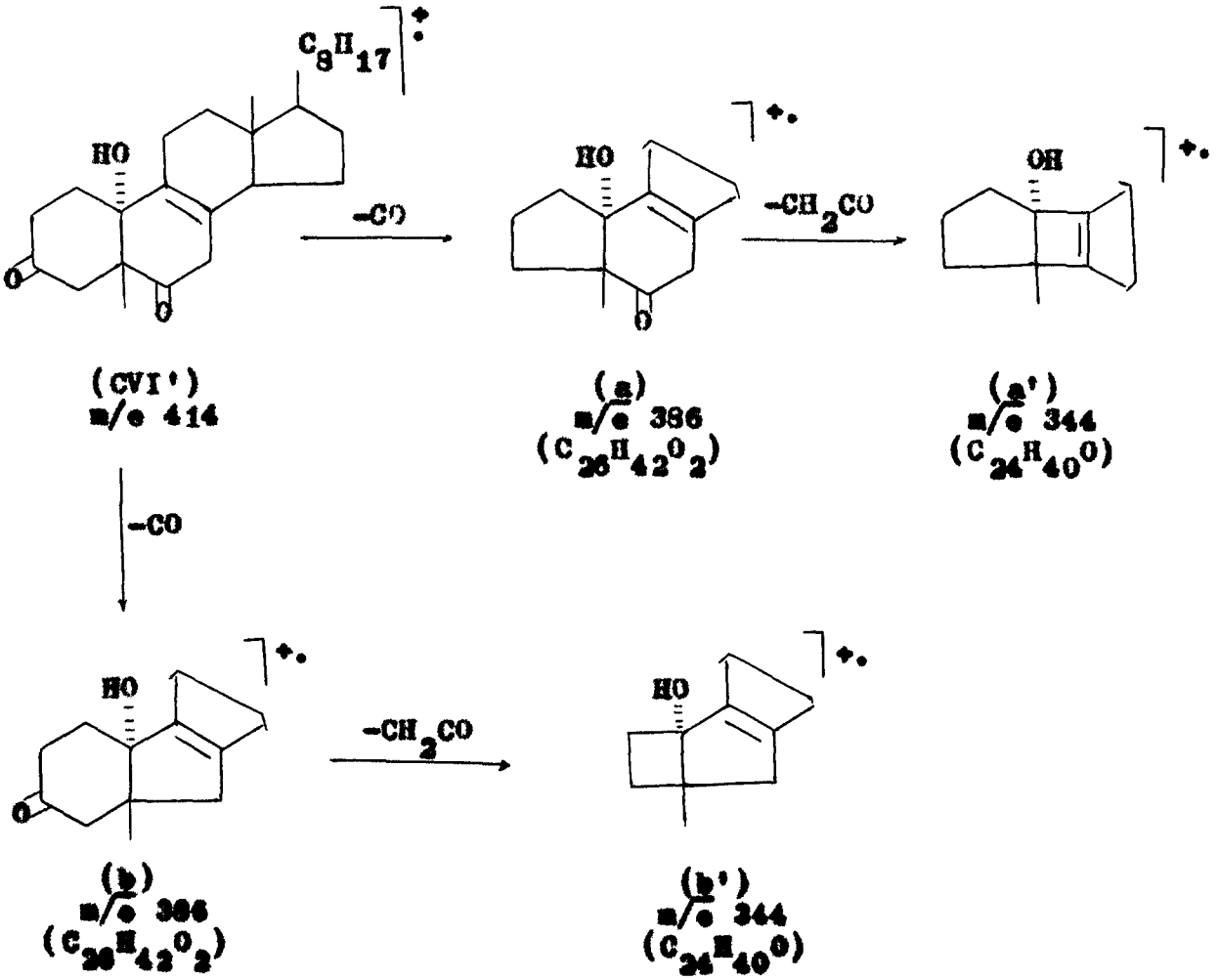


Fig.1 MASS SPECTRUM OF (CVI)

m/e 396 ($M^{+\cdot}$ $-H_2O$), m/e 386 ($M^{+\cdot}$ $-CO$), m/e 381 (m/e 396-CH_3), m/e 372 ($M^{+\cdot}$ $-CH_2CO$), m/e 354 (m/e 396-CH_2CO), m/e 344 ($M^{+\cdot}$ $-C_4H_6O$), m/e 330 ($M^{+\cdot}$ - $2CH_2CO$), m/e 316 (m/e 344-CO), m/e 301 ($M^{+\cdot}$ $-C_8H_{17}$), m/e 283 (m/e 301 - H_2O), m/e 255 (m/e 283-CO), m/e 241 (m/e 283-CH_2CO), m/e 217 (m/e 301-$2CH_2CO$) and other lower mass peaks.

m/e 386 and 344

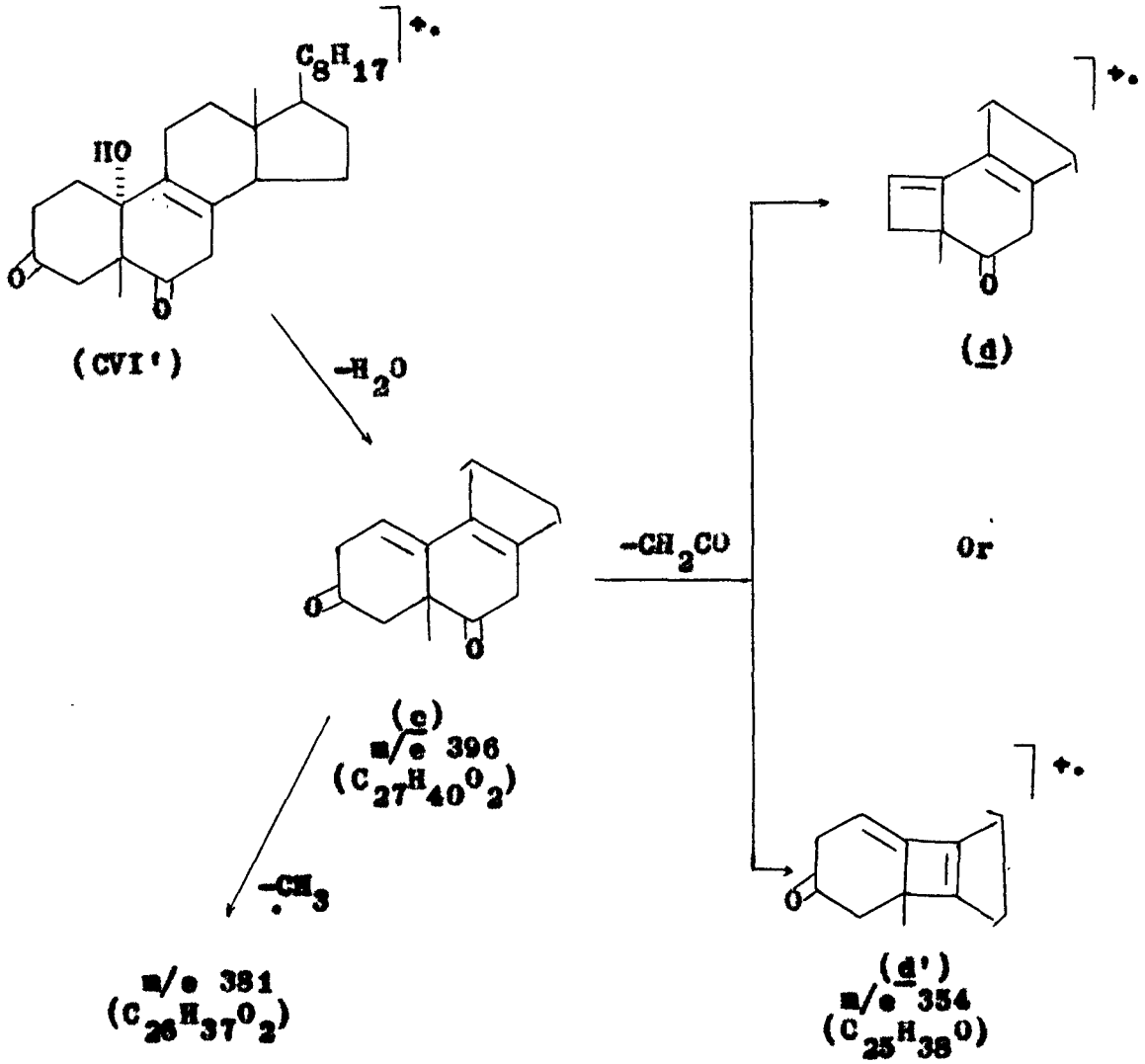
The composition of the ions m/e 386 (a or b) and 344 (a' or b' suggested that these ions are originated by the loss of CO and CH_2CO from the molecular ion either from ring A or B (Scheme - 1).



Scheme - 1

m/e 396, 381 and 354

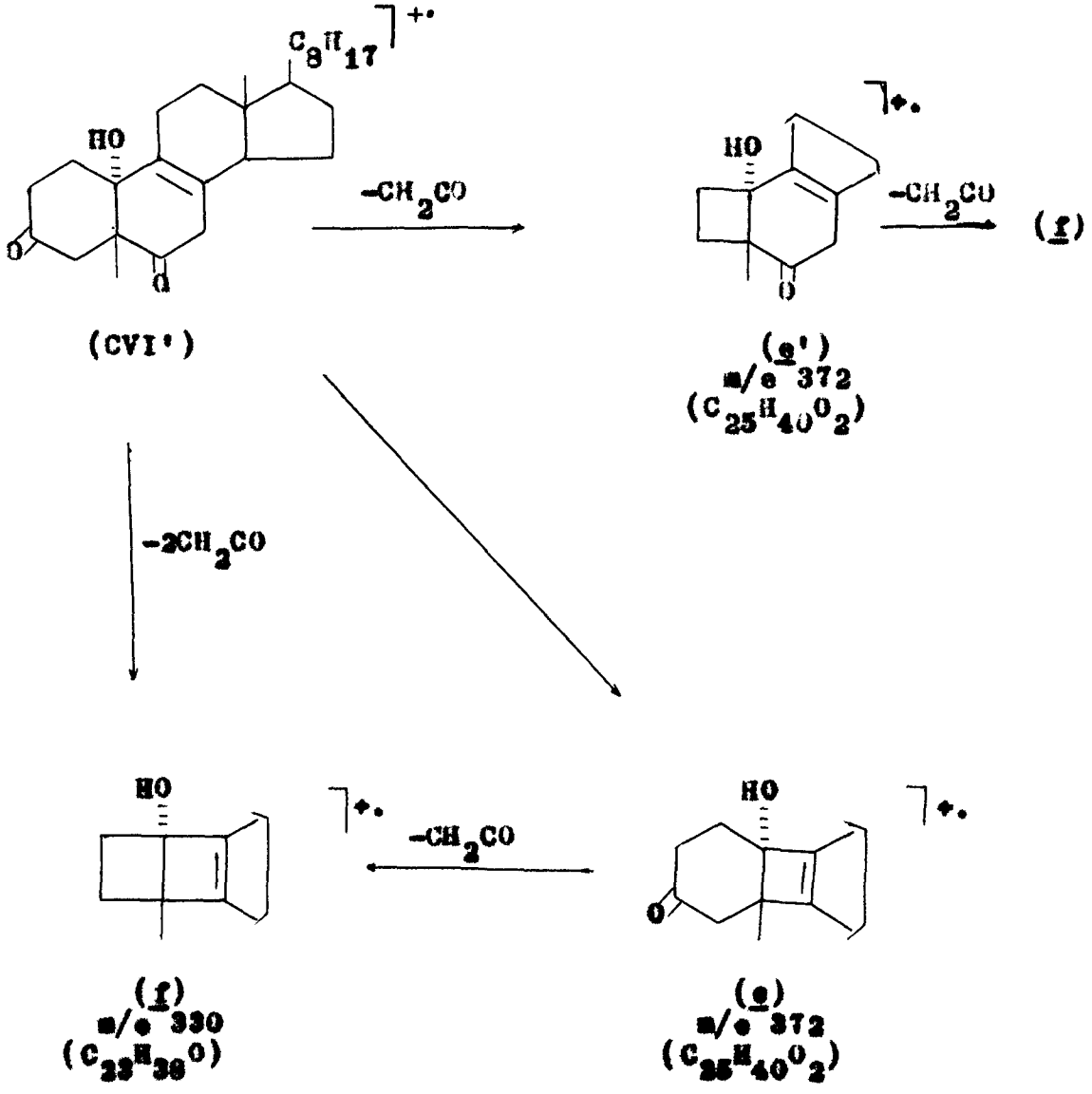
The fragment ion m/e 396 obviously results by the loss of a molecule of water from the molecular ion (CVI). The fragment ions m/e 381 and 354 (d or d') can be rationalized by the assumption that methyl radical and a molecule of ketene are ejected from the ion (e) respectively.



Scheme - 2

m/e 372 and 330

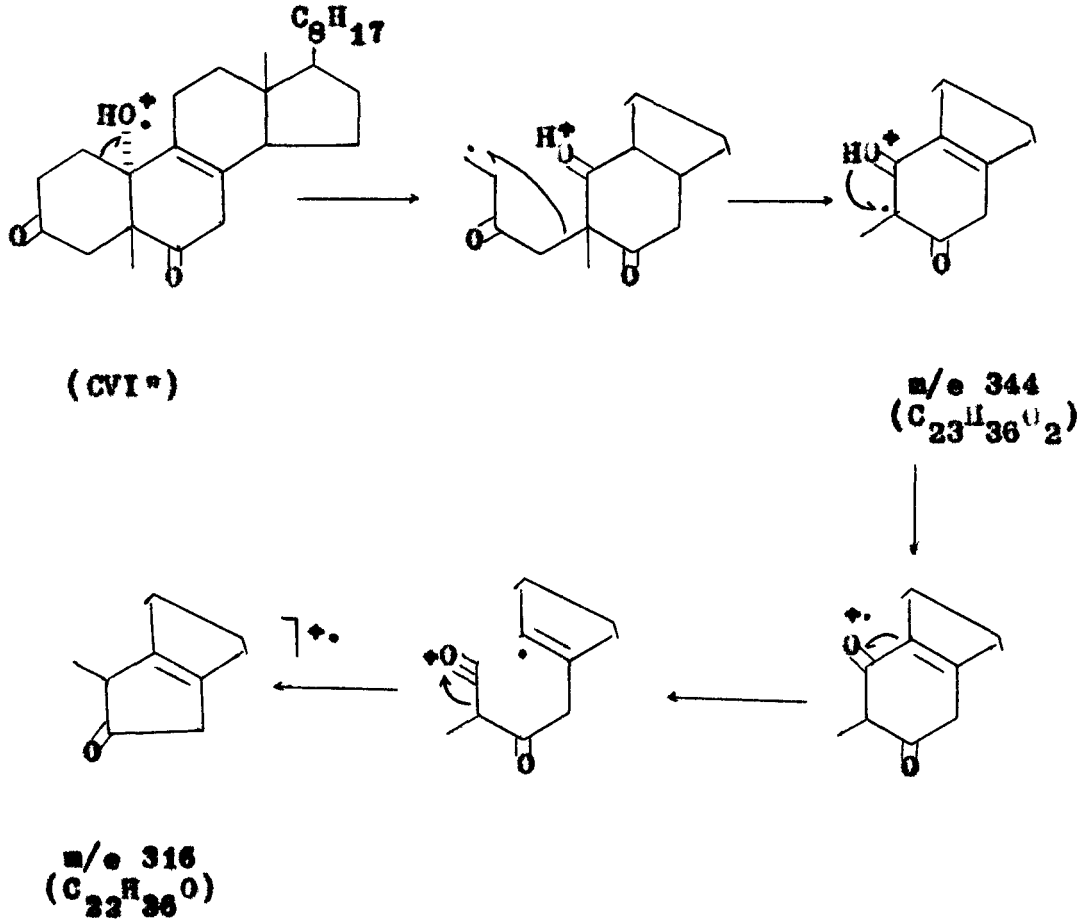
The fragment ion m/e 372(e or e')may arise by the loss of a ketene molecule either from ring A or B of (CVI') which further loses a molecule of ketene giving ion m/e 330 (f). Formation of (f) also can be shown by the loss of two molecule of CH_2CO from molecular ion (Scheme - 3).



Scheme - 3

m/e 344 and 316

The ions m/e 344 and 316 arising from molecular ion (CVI•) are depicted in Scheme - 4.



(CVI•)

m/e 344
($C_{23}H_{36}O_2$)

m/e 316
($C_{22}H_{36}O$)

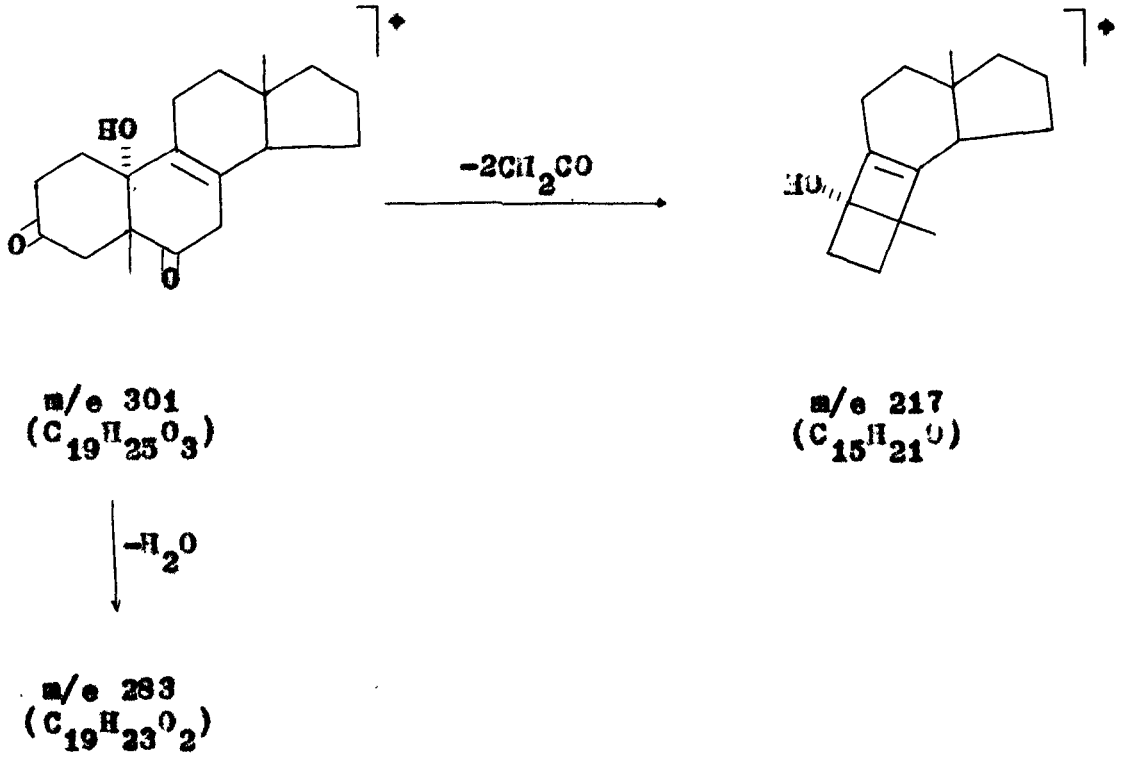
Scheme - 4

m/e 301

The fragmentation is compatible with the loss of the side chain (C_8H_{17}) from parent peak ($M^{+\bullet}$ 414).

m/e 283 and 217

The ion peaks m/e 283 and 217 arise from m/e 301 by the loss of H_2O and two ketene molecules respectively (Scheme - 5).

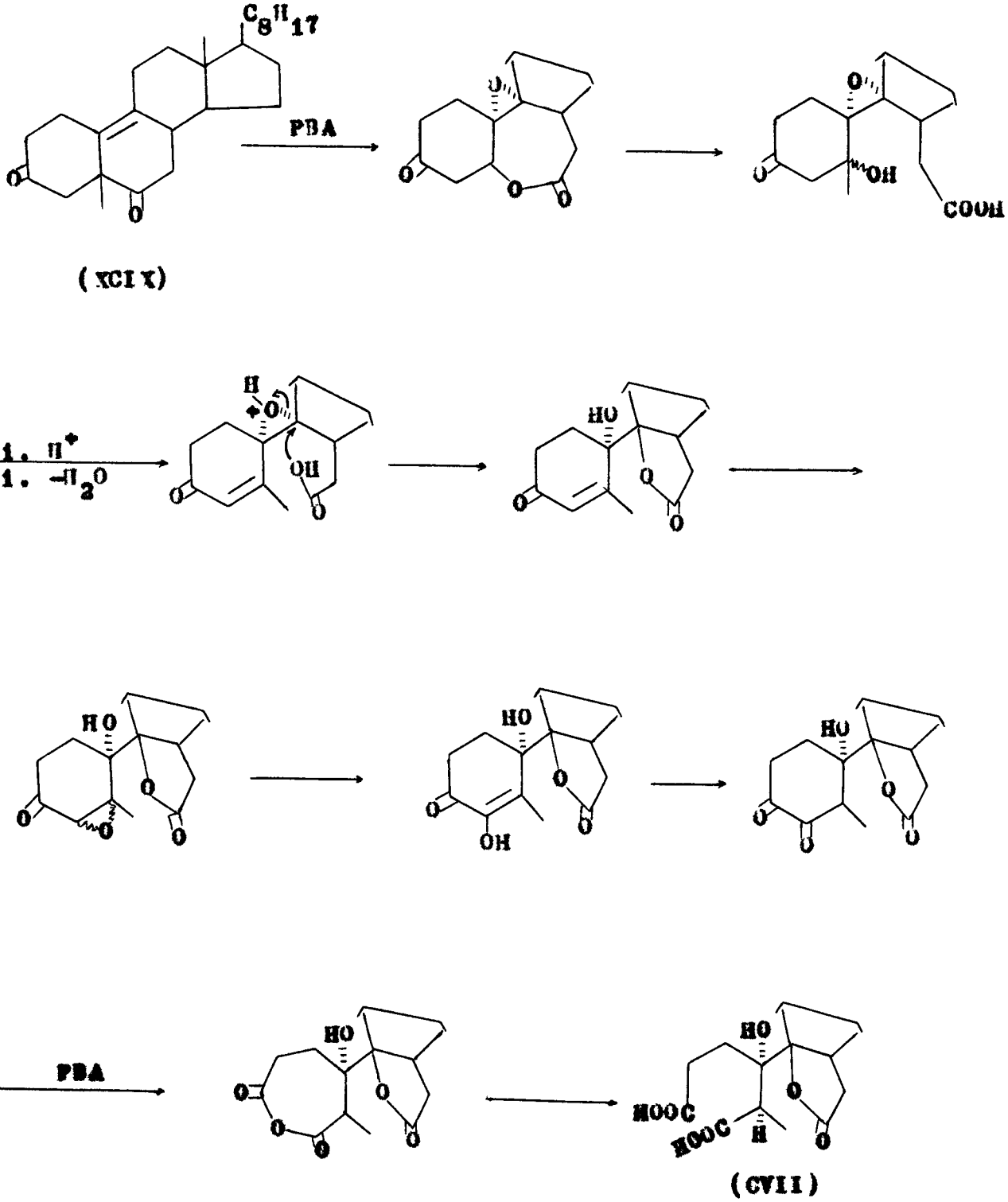


Scheme - 5

Characterisation of oil, as 5-methyl-19-nor-9β,10α-dihydroxy-3,4,5,6-disecocholest-6-oic acid 6,9-lactone (CVII)

The oil was analysed correctly for $C_{27}H_{44}O_7$. The IR spectrum exhibited absorption bands at 3650s (3^0 OH), 3450(COOH), 1785 (γ-lactone) and 1720 cm^{-1} (COOH). NMR spectrum of (CVII) gave a multiplet at δ 7.45 integrating for 2 protons ascribable to C3 and C4 carboxyl protons (exchangeable with deuterium). The angular and side chain methyl protons were appeared at δ 0.93 and 0.83.

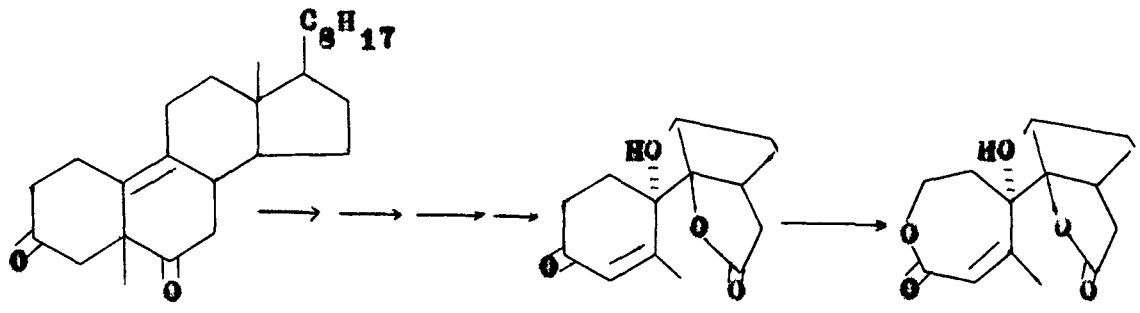
The mechanism for the formation of (CVII) from (XCIX) has been suggested (Scheme - 6).



Sch - 6

Characterization of the compound, m.p. 178° as 19-nor-3-oxa-4-keto-5α-methyl-9β,10α-dihydroxy-5,6-seco-A-homocholest-5-en-6-oic acid 6,9-lactone (CVIII)

The compound, m.p. 178° was analyzed for $C_{27}H_{42}O_5$ ($M^{+\cdot}$ 446). The elemental composition suggested that the reaction has gone beyond normal Baeyer-Villiger stage. The UV absorption maximum at 230 nm showed the presence of an α,β -unsaturated carbonyl chromophore. It was further supported by the IR spectrum where a strong band at 1695 cm^{-1} was observed for (C=C-C=O). Other bands were seen at 3418s (3° OH), 1770 cm^{-1} (γ-lactone). N.M.R. spectrum exhibited a singlet at δ 5.2 which was assigned to vinylic proton (C4a-H). A singlet at δ 2.56 integrating for 3 protons was ascribable to C5-CH_3. The shift of C5-methyl protons in the downfield region indicated that the methyl group is vinylic in nature. A multiplet centred at δ 4.0 integrating for two protons was assigned to (CH_2-O-). Other signals were appeared at δ 0.68 (C13-CH_3), 0.91 and 0.83 (remaining methyl protons). Formation of (CVIII) from (XCIX) can be explained as follows (Scheme - 7).



(XCIX) (CVIII)

Scheme - 7

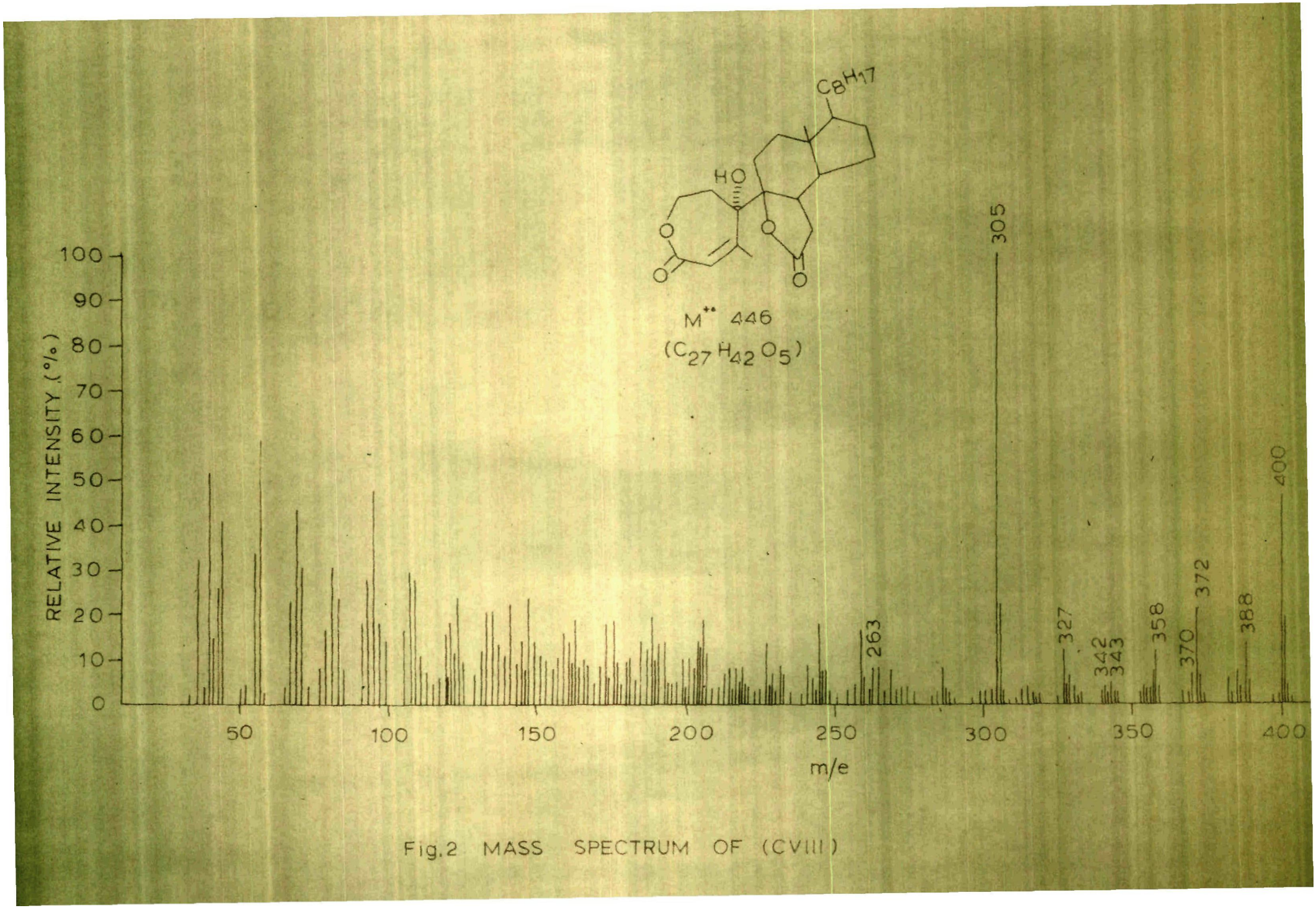
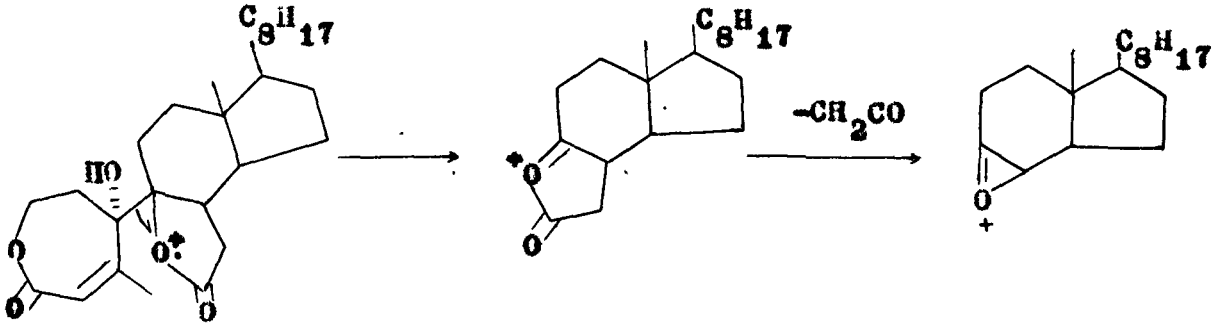


Fig.2 MASS SPECTRUM OF (CVIII)

The mass spectrum of (CVIII)(Fig. 2) gave molecular ion peak at m/e 446 ($C_{27}H_{42}O_5$). The other diagnostic peaks were m/e 418 ($M^{+\cdot}$ -CO), m/e 400 (m/e 418-H_2O), m/e 388 (m/e 418-CH_2O), m/e 370 (m/e 400-CH_2O), m/e 385 (m/e 400-CH_3), m/e 358(m/e 400-CH_2CO), m/e 372 (m/e 400-CO), m/e 342 (m/e 372-CH_2O), m/e 327 (m/e 342-CH_3), m/e 305 (base peak), m/e 287, m/e 263, m/e 259, m/e 245, m/e 141, m/e 123 and lower mass peaks.

m/e 305 and 263

The base peak at m/e 305 was very helpful in structure elucidation. The fragment ion m/e 263 arises by the loss of CH_2CO from base peak (g).

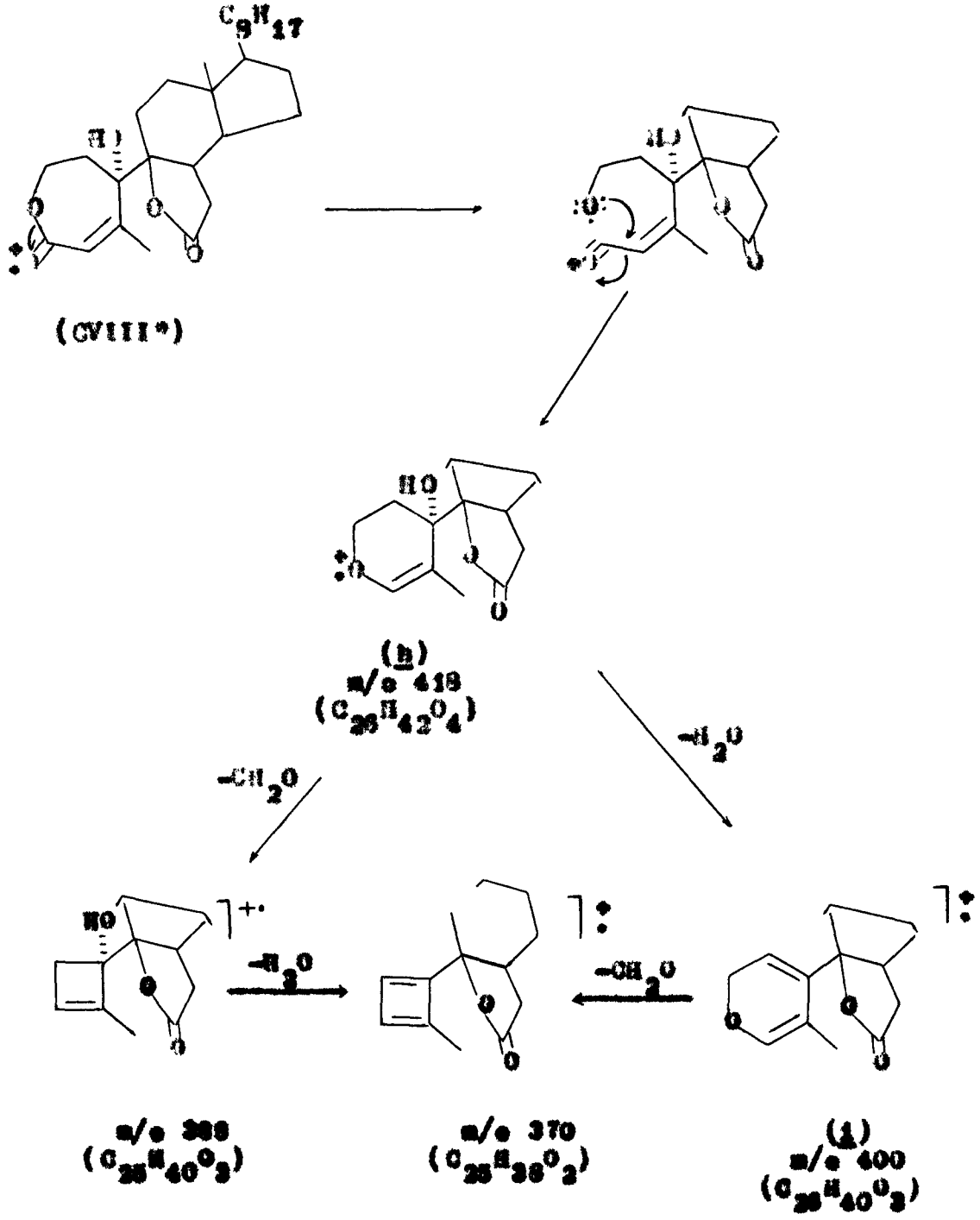


(CVIII') (g) m/e 305 ($C_{20}H_{33}O_2$) m/e 263 ($C_{18}H_{31}O$)

Scheme - 8

m/e 418, 400, 398 and 370

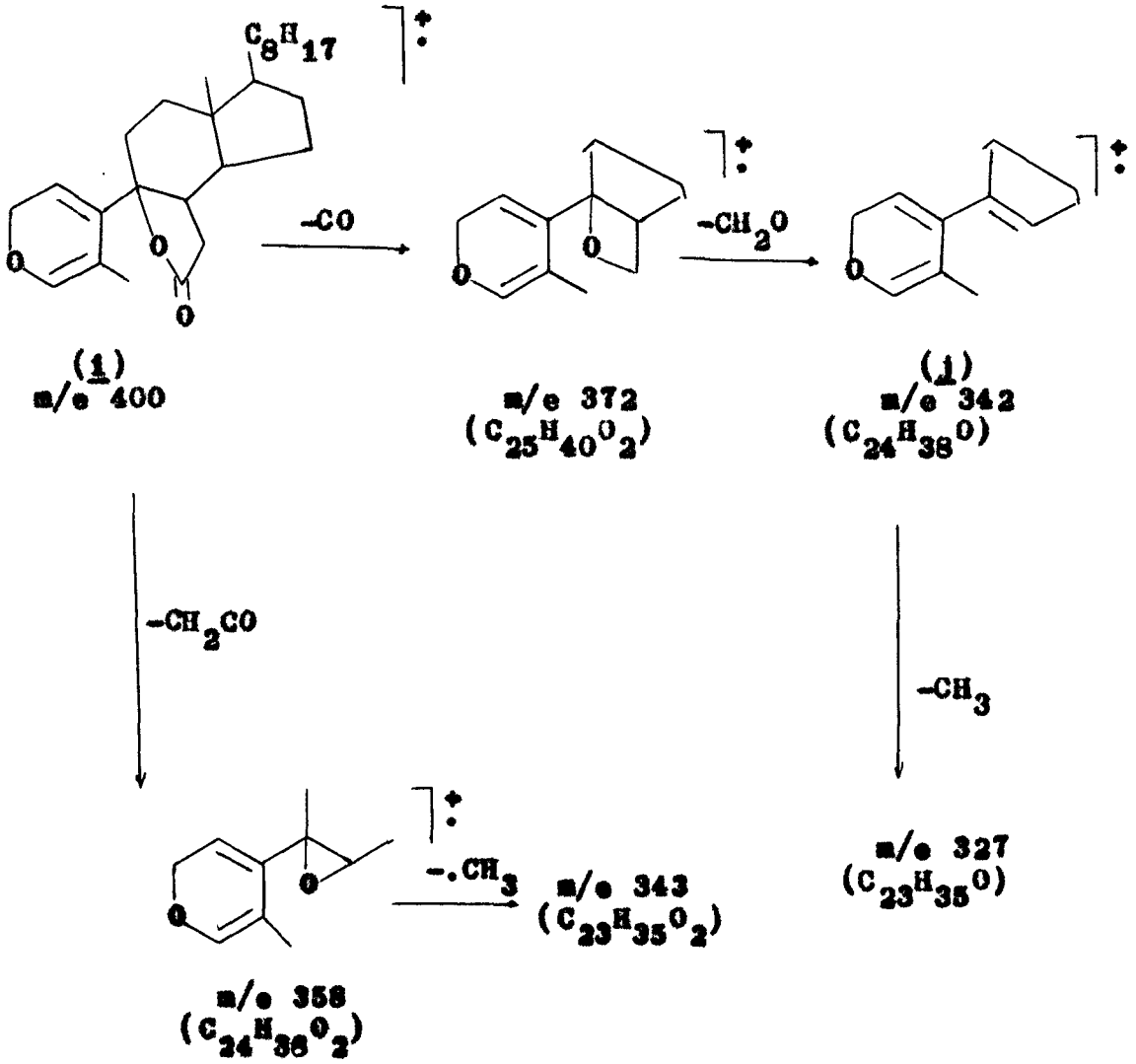
These fragment ions generating from the molecular ion (CVIII") can be shown according to Scheme - 9.



Scheme - 9

m/e 372, 358, 343, 342 and 327

The ions m/e 372 and 342 can be conveniently shown by the loss of CO and CH_2O from ion 1 respectively and subsequent loss of methyl radical from (1) will result ion m/e 327. Similarly m/e 343 may result with the loss of CH_2CO and CH_3 from ion 1 (Scheme - 10).

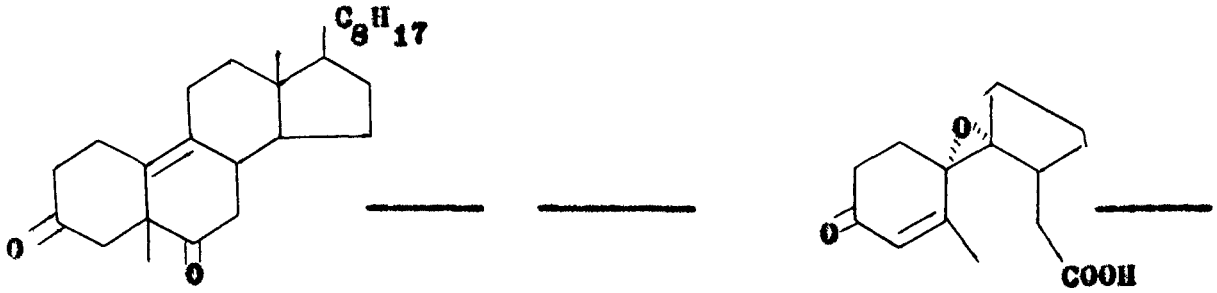


Scheme - 10

Characterisation of the compound, m.p. 170° as 19-nor-4,6-dioxa-3,5,6a-triketo-5a-methyl-10α-hydroxy-A,B-bishomocholest-9(9)-ene (CIX)

The compound melting at 170° was analysed for $C_{27}H_{40}O_6$ ($M^{+\cdot}$ 460)(+ve tetranitromethane test). The I.R. spectrum displayed bands at 3330s (3^{o} OH), 1785, 1750 and 1705 cm^{-1}. The bands at 1785 and 1750 cm^{-1} are characteristic for acid anhydride and 1705 cm^{-1} signifies the presence of ϵ-lactone. N.M.R. spectrum of the compound showed a multiplet centred at δ3.2 integrating for 4 protons which were ascribed to α-methylene protons (4H: C7-$\underline{H}_2$, C2-$\underline{H}_2$). No other signals were seen in the downfield region. Other signals were observed at δ1.0 (C5-$C\underline{H}_3$), 0.7 (C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

To account for the formation of (CIX) from (XCIX), a mechanism has been proposed (Scheme - 11).



(XCIX)

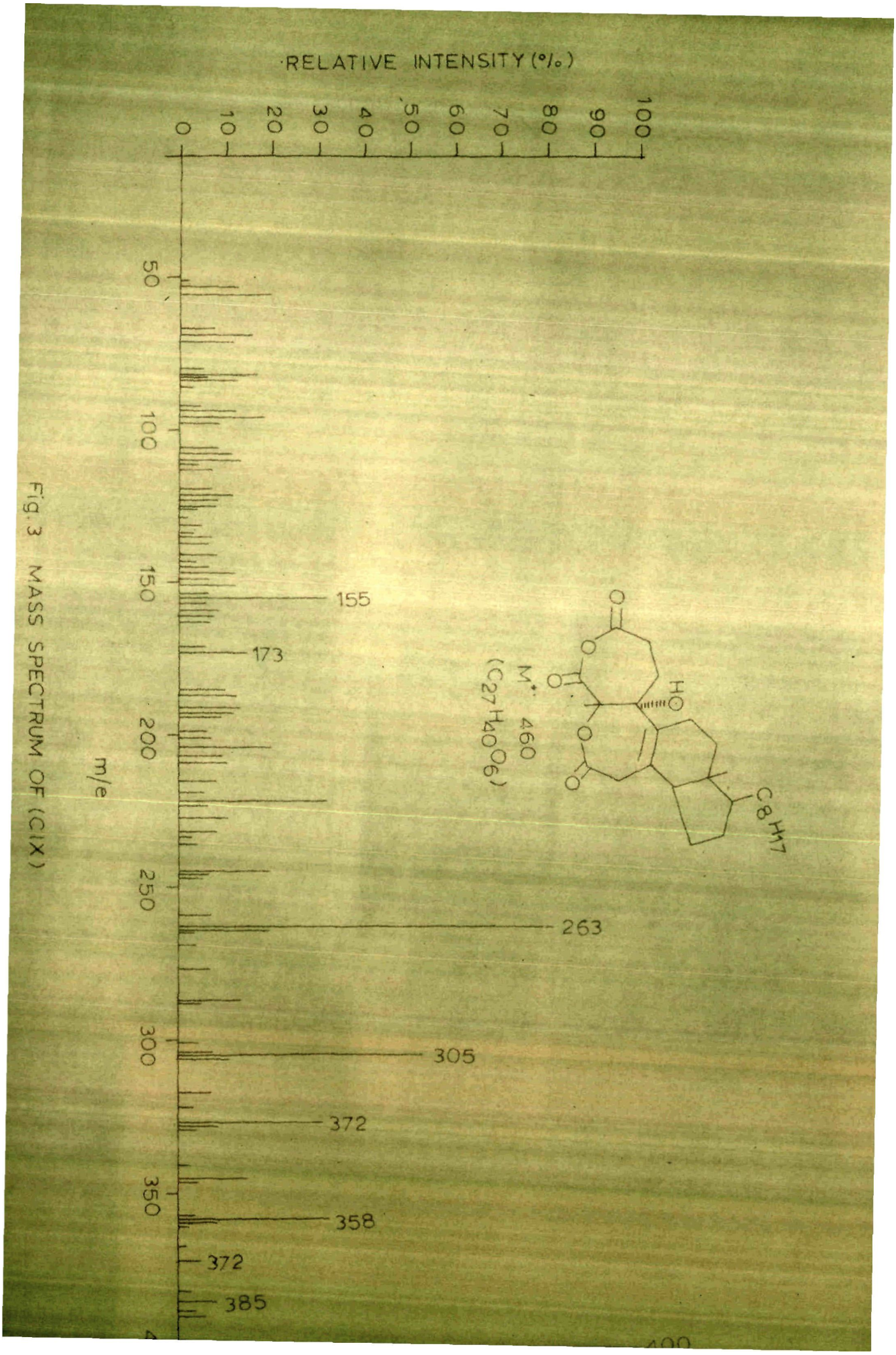
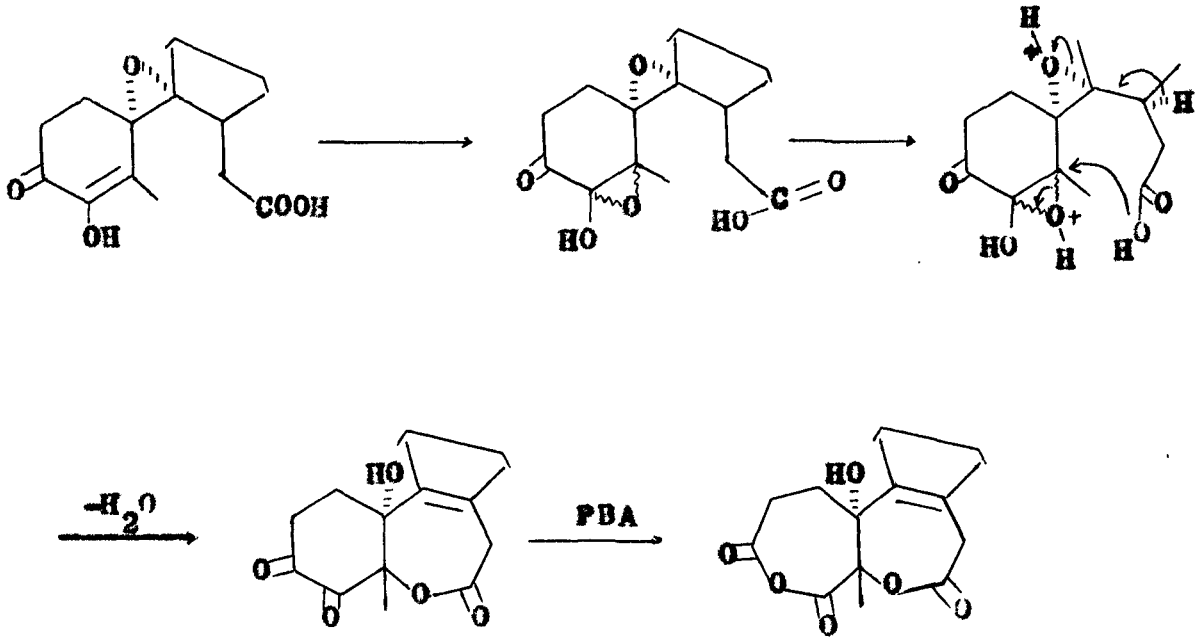


Fig. 3 MASS SPECTRUM OF (CIX)



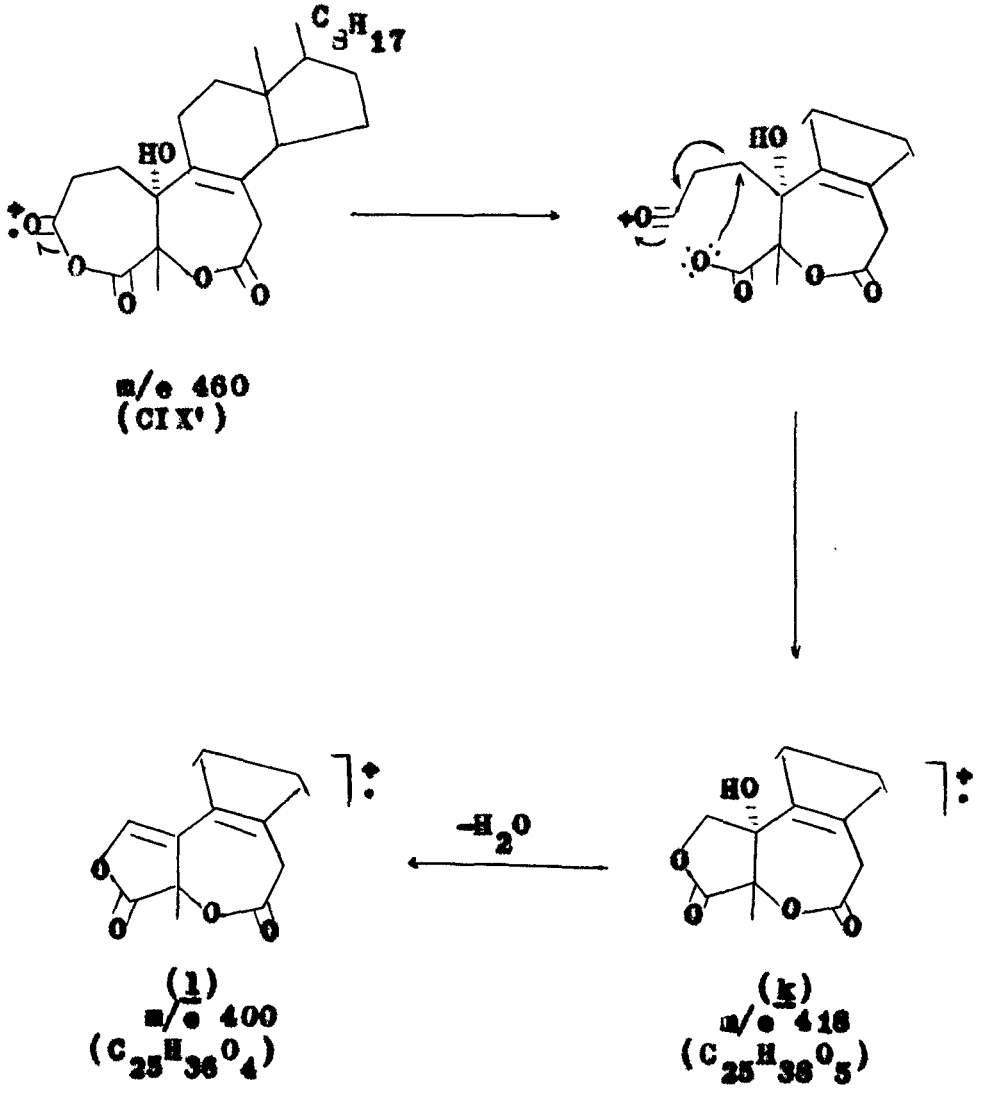
(CIX)

Scheme - 11

Further evidence in support of the compound melting at 170° was given by mass spectral studies. The (CIX) (Fig. 3) showed molecular ion peak at m/e 460. The other significant peaks were at m/e 418 ($M^{+\cdot}$ $-CH_2CO$), m/e 400 (m/e 418-H_2O, base peak), m/e 390 (m/e 418-CO), m/e 385 (m/e 400-CH_3), m/e 372 (m/e 400-CO), m/e 358 (m/e 400-CH_2CO), m/e 305, m/e 287, m/e 277, m/e 263, m/e 173, m/e 155, m/e 113 and lower mass peaks.

m/e 418 and 400

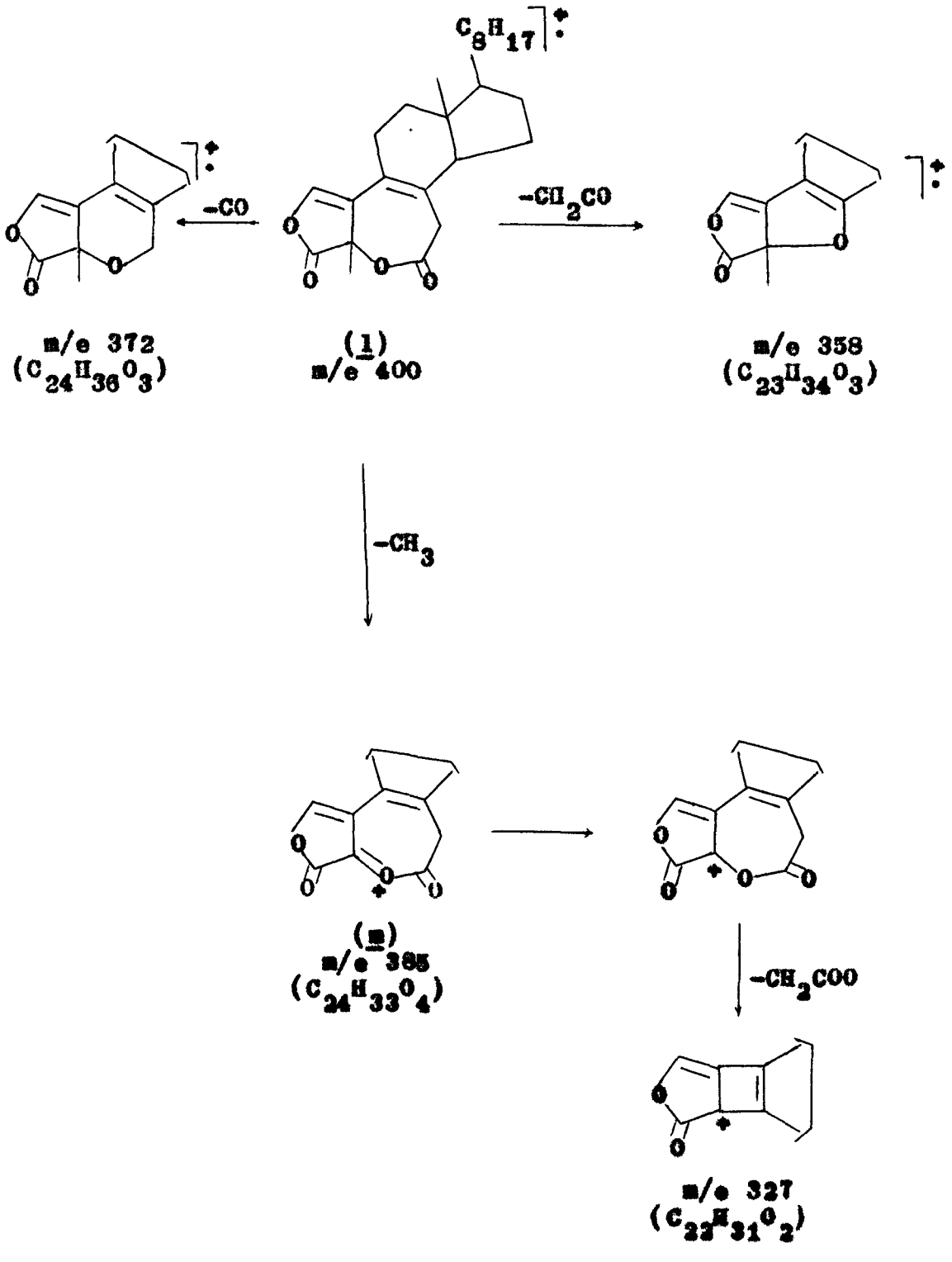
The fragment ions m/e 418 and 400 arising from (CIX') can be shown as follows (Scheme - 12).

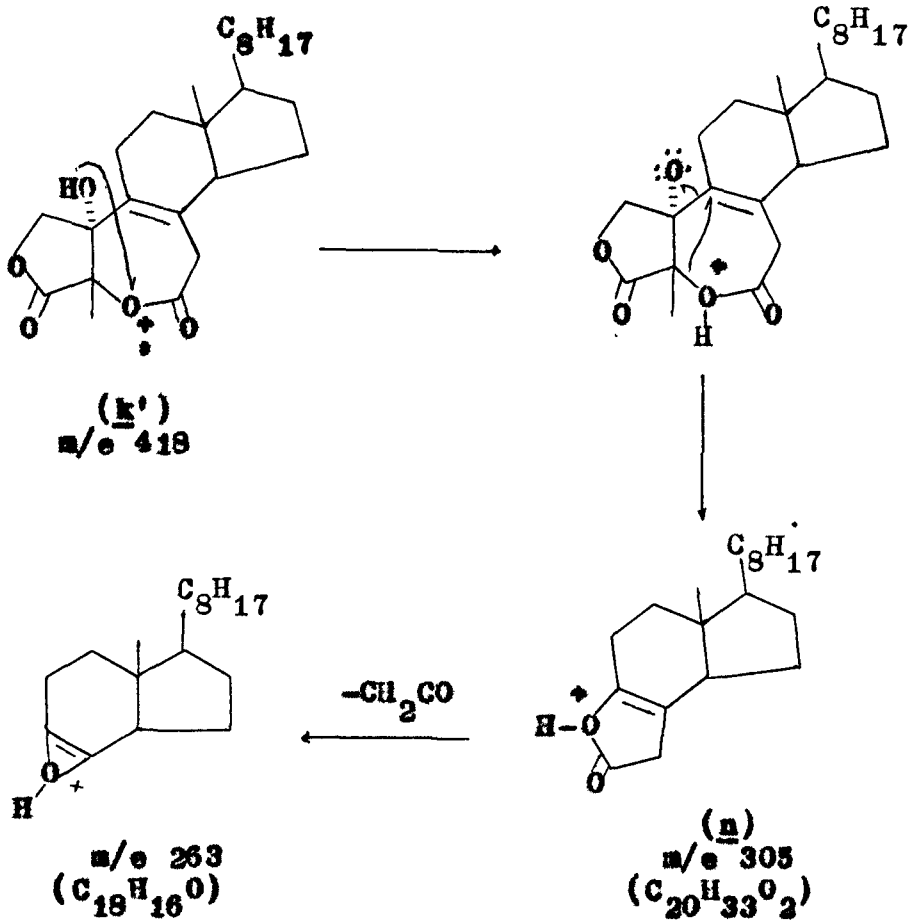


Scheme - 12

m/e 385, 372, 358, 327, 305 and 263

The formation of these ions can be shown according to Scheme - 13.





(k')
m/e 418

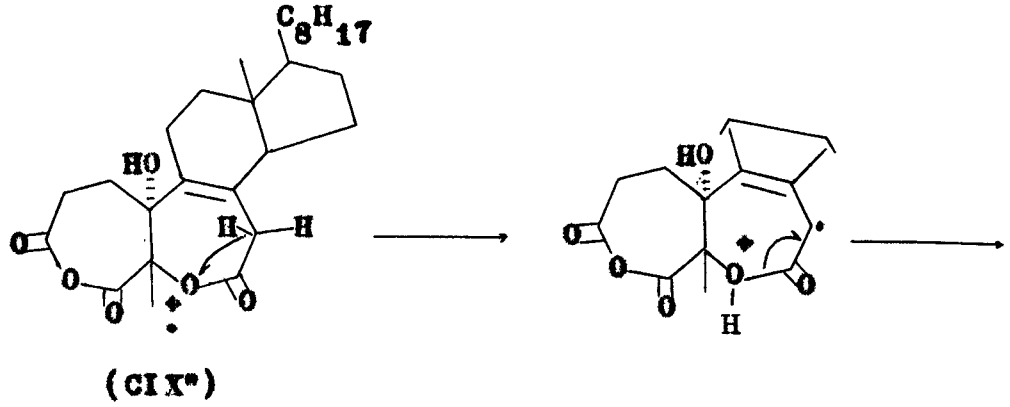
(n)
m/e 305
($C_{20}H_{33}O_2$)

m/e 263
($C_{18}H_{16}O$)

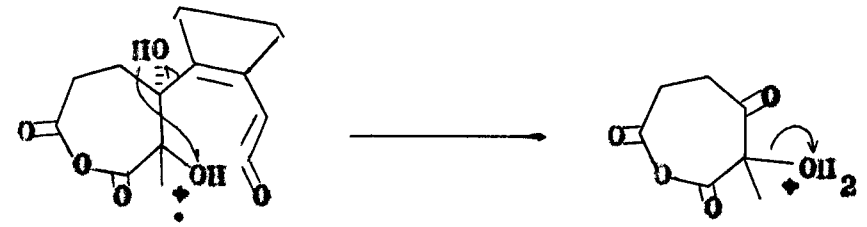
Scheme - 13

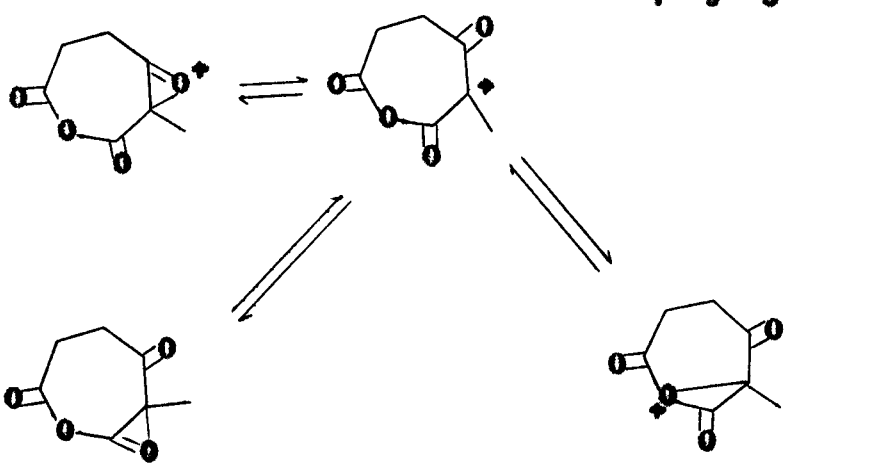
m/e 173 and 155

The loss of mass unit 287 from the precedence molecular ion ($CIX^{\bullet}$) has been suggested accordingly to Scheme - 14. Further loss of H_2O gave m/e 155.



(CIX[m])





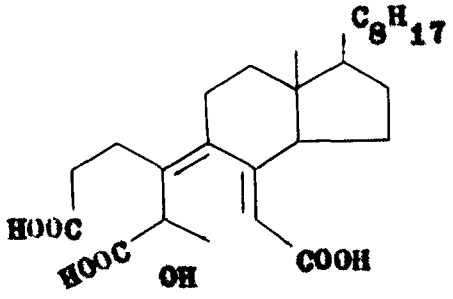
(o)
m/e 173
($C_7H_9O_5$)

m/e 155
($C_7H_7O_4$)

Scheme - 14

Base hydrolysis of (CIX) : 19-nor-5-methyl-5-hydroxy-3,4,5,6-disecocholest-7(8), 9(10)-dien-2,5,7-tricarboxylic acid (CX)

The mixture of (CIX)(0.1 g) and 5% methanolic potassium hydroxide (20 ml) was refluxed on water bath for 2 hrs. The reaction mixture was poured into excess of water, acidified with dil HCl and extracted with ether. Usual workup and removal of solvent gave (CX) as a non-crystallizable oil. The seco acid (CX) was correctly analysed for $C_{27}H_{42}O_7$. I.R. spectrum exhibited bands at 3650 (sharp; 3° OH), 3400br (COOH), 1710s (COOH), 1660 (C=C-C=C-CO), 1620 cm^{-1} (C=C). N.M.R. spectrum of (CX) displayed a broad signal at δ 6.7 integrating for 4 protons (C2-COOH + C5-COOH + C5-OH and C7-H). On deuterium shake a sharp singlet at δ 6.7 for one proton was observed for vinylic proton (C7-H). The other signals were appeared at δ 1.26 ($C5-CH_3$), 0.9 and 0.82 (remaining methyl protons).



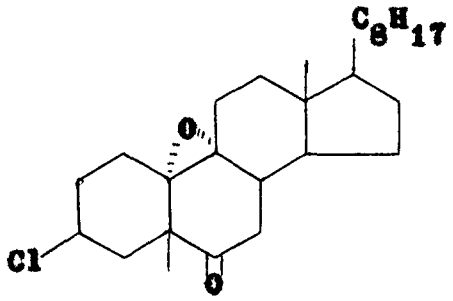
(CX)

Baeyer-Villiger oxidation of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (C)

The ketone (C) was treated with perbenzoic acid (2.5 mole equivalent) in the presence of p-toluenesulphonic acid as catalyst. After usual workup and column chromatography over silica gel two compounds, m.p. 138° and 105° were obtained.

Characterization of the compound, m.p. 138° as 3β-chloro-19-nor-5-methyl-9α,10α-epoxy-5β-cholestan-6-one (CXI)

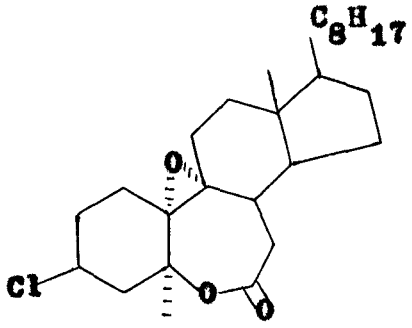
The compound, m.p. 138° was analysed for $C_{27}H_{43}O_2Cl$. The molecular composition showed the addition of one oxygen atom to the substrate (C). I.R. spectrum revealed the absorption band at 1700 (C=O), 900 (epoxide) and 715 cm^{-1} (C-Cl). N.M.R. spectrum of the compound showed a multiplet at δ 4.6 integrating for one proton which has been assigned to (C3-αH; $W_{\frac{1}{2}}$ = 15 Hz); indicating the A/B ring junction trans. The other signals were appeared at δ 1.26 (C5-CH_3), 0.75 (C13-CH_3), 0.88 and 0.80 (remaining methyl protons).



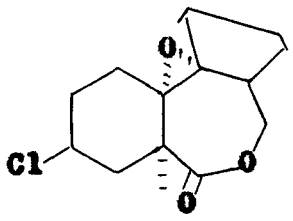
(CXI)

Characterisation of the compound, m.p. 105° as 3β-chloro-6-oxa-19-nor-5α-methyl-9α,10α-epoxy-B-homocholestan-7-one(CXII)

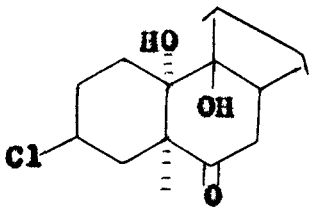
The compound, m.p. 105° was correctly analysed for $C_{27}H_{43}O_3Cl$ (positive Beilstein test). The molecular composition showed the addition of two oxygen atoms to the substrate (C). Three possible structures (CXII-CXIV) can be written for the compound under discussion. The I.R. spectrum of the compound exhibited bands at 1705 (∈-lactone), 895 (epoxide) and 705 cm^{-1} (C-Cl). The absence of absorption band for OH discarded the structure (CXIV). N.M.R. spectrum gave a multiplet at δ 3.7 integrating for one proton having half band width 6 Hz, was assigned to C3-αH(equatorial; cis A/B ring junction).



(CXII)



(CXIII)



(CXIV)

From this observation, it is evidenced that the stereochemistry of the C5-methyl has been changed during the course of reaction. This could be in sharp contrast to the accepted mode in which stereochemistry of the migrating carbon remains unaltered. No

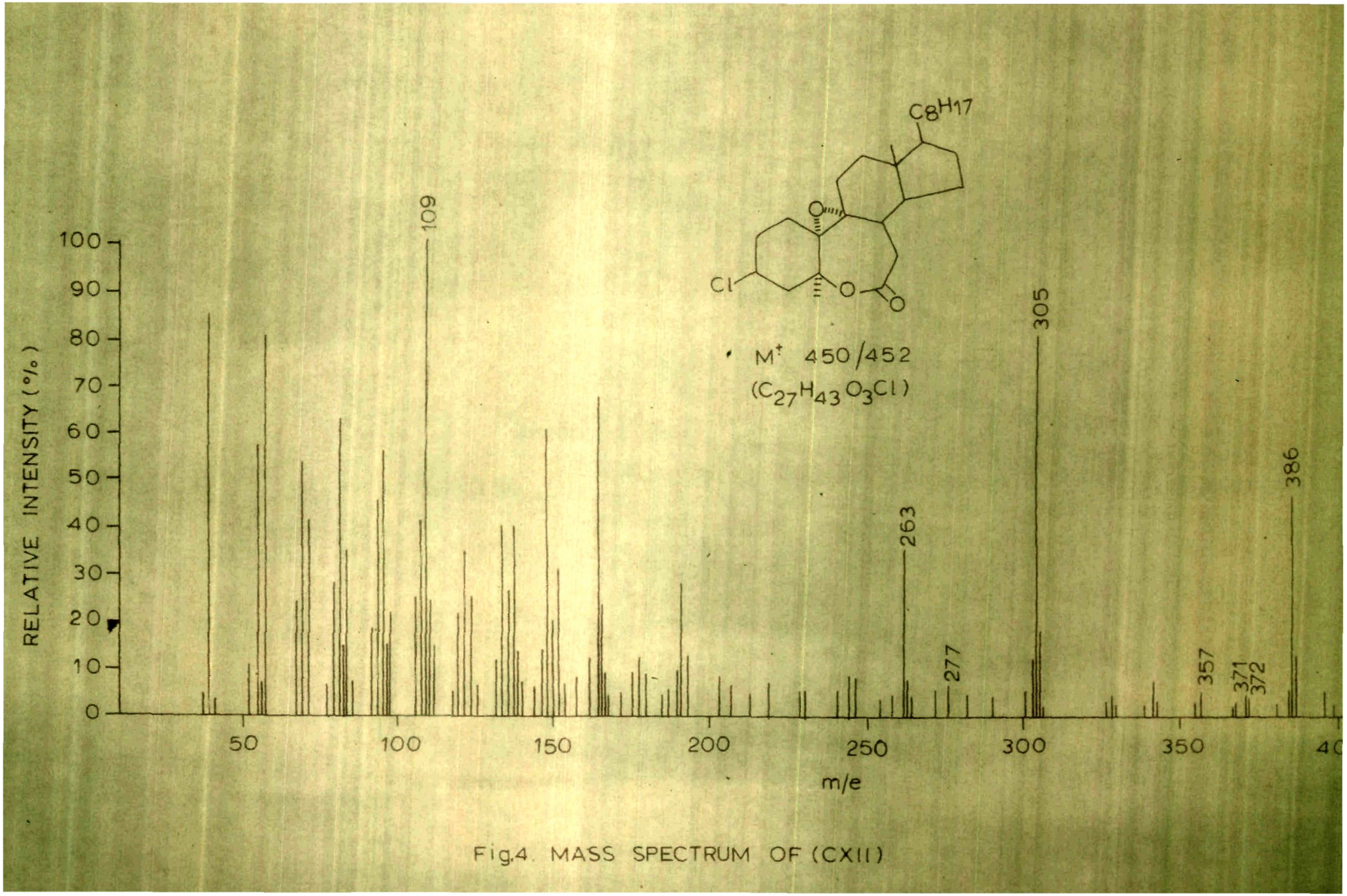


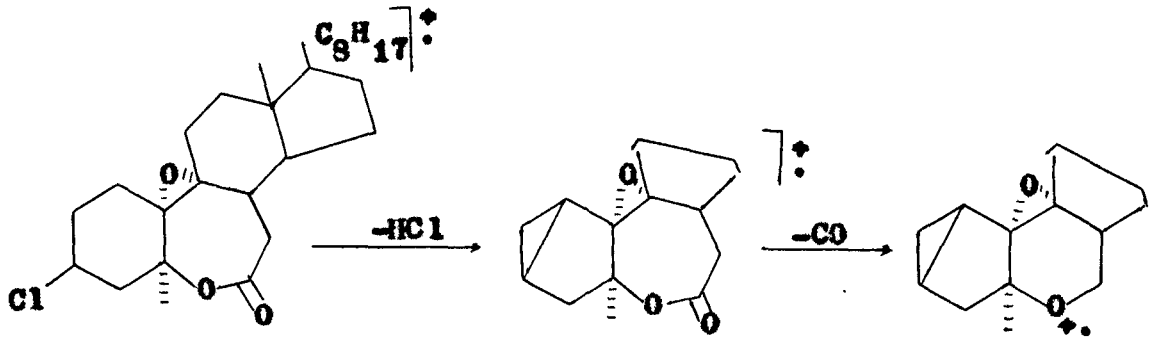
Fig.4 MASS SPECTRUM OF (CXII)

other signal was found in the downfield region (δ 4-5), supporting the structure (CXII). Other signals were at δ 1.35 (C5-$\underline{CH}_3$), 0.73 (C13-$\underline{CH}_3$), 0.9 and 0.8 (remaining methyl protons).

Further evidence in support of structure (CXII) was found by mass spectrum. The compound (CXII)(Fig. 4) showed molecular ion peaks at m/e 450/452 along with significant peaks at m/e 414 ($M^{+\cdot}$ -HCl), m/e 386 (m/e 414-CO), m/e 372 (m/e 414-CH_2CO), m/e 371 (m/e 386-CH_3), m/e 357 (m/e 372-CH_3), m/e 305, m/e 277, m/e 263, m/e 245, m/e 109 (base peak), m/e 91 and lower mass peaks.

m/e 414, 386 and 371

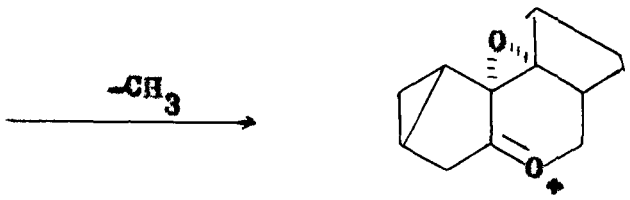
The loss of HCl giving ion peak m/e 414 (p) occurs mainly by 1,3-elimination process[31] and it appears that in doing so cyclopropane derivative is obtained. The loss of CO from the ion p may be shown to occur as in Scheme - 15, resulting m/e 386 (q). Further loss of a methyl group from the ion q gives rise to the ion m/e 371.



(CXII') m/e 450/452 ($C_{27}H_{43}O_3Cl$)

(p) m/e 414 ($C_{27}H_{42}O_3$)

(q) m/e 386 ($C_{26}H_{42}O_2$)

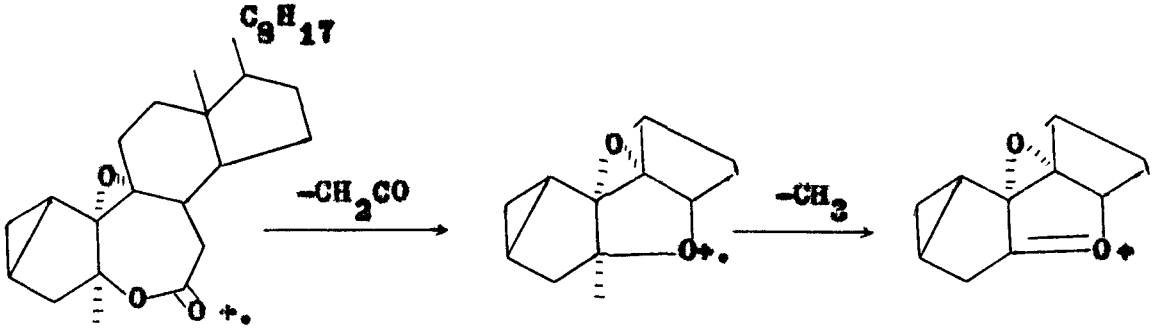


m/e 371
($C_{25}H_{39}O_2$)

Scheme - 15

m/e 372 and 357

Formation of ion peak m/e 372 (r) is due to elimination of a ketene molecule from m/e 414 (p') shown accordingly (Scheme - 16). Subsequent loss of CH_3 radical from ion r provides the ion m/e 357.



(p')

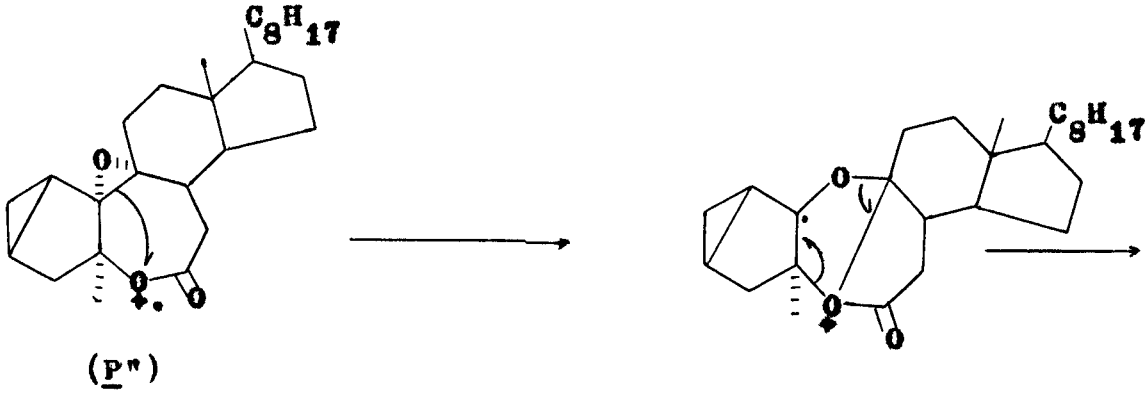
(r)
m/e 372
($C_{25}H_{40}O_2$)

m/e 357
($C_{24}H_{37}O_2$)

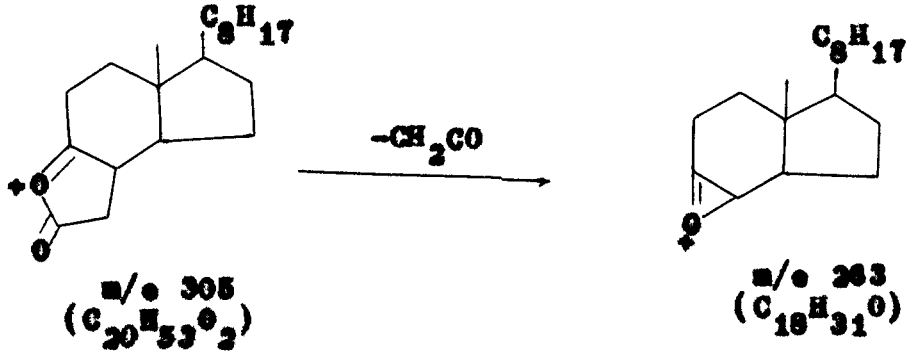
Scheme - 16

m/e 305, 263 and 109 (base peak)

The loss of mass unit 109 from m/e 414 (p") gave m/e 305 which loses CH_2CO forming ion m/e 263. The formation of the base peak (C_7H_9O) is depicted in Scheme - 17.

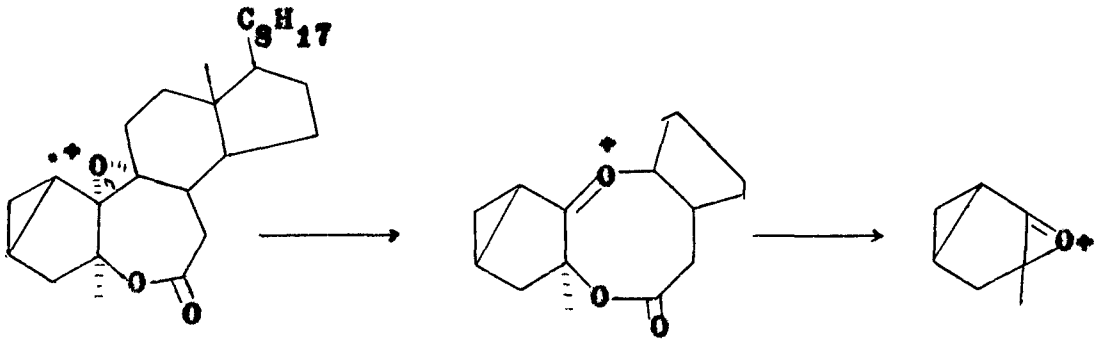


(P")



m/e 305
($C_{20}H_{33}O_2$)

m/e 263
($C_{18}H_{31}O$)



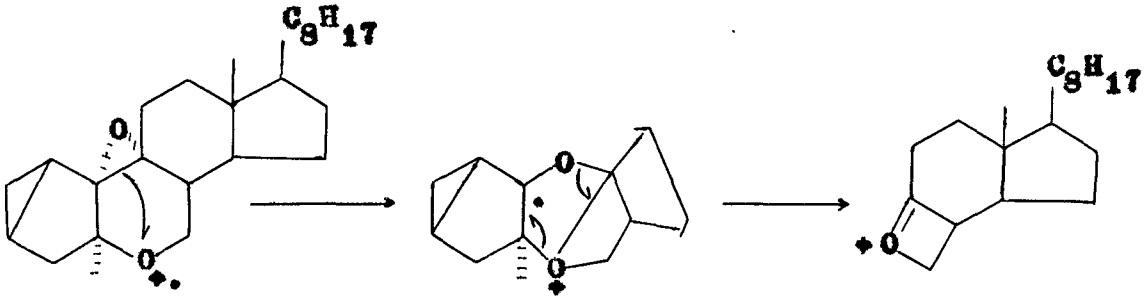
(p'')

m/e 109
(C_7H_9O)

Scheme - 17

m/e 277

The formation of ion m/e 277 is depicted in Scheme - 18.



(r)

m/e 277
($C_{19}H_{33}O$)

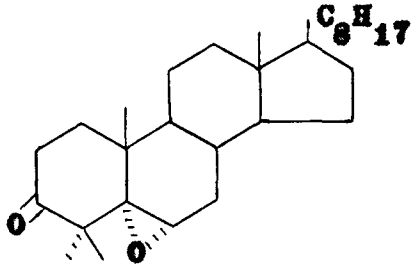
Scheme - 18

Baeyer-Villiger oxidation of 4,4-dimethylcholest-5-en-3-one (CI)

The solution of ketone (CI) in chloroform was treated with perbenzoic acid (1.1 mole equivalent) in the presence of p-toluenesulphonic acid as catalyst. The reaction mixture was worked up in the usual manner as described earlier. Residue obtained was chromatographed over silica gel which provided two compounds, m.p. 144° and 187°.

Characterization of the compound, m.p. 144° as 5,6α-epoxy-4,4-dimethyl-5α-cholestan-3-one (CXV)

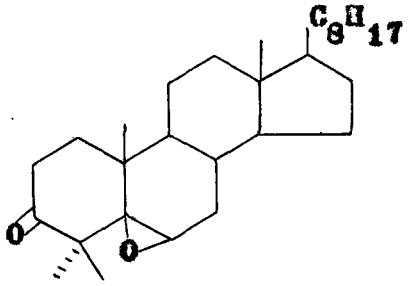
The compound, m.p. 144° was analysed for $C_{29}H_{49}O_2$. The molecular composition showed the addition of an oxygen atom to the parent ketone (CI). In the I.R. spectrum bands were seen at 1710 (C=O), and 720 cm^{-1} (epoxide). No band for double bond was observed. In N.M.R. spectrum a doublet at δ 2.93 (J_{ae} = 5 Hz) was revealed integrating for one proton which was assigned to C6-$\beta\underline{H}$. Methyl protons were observed at δ 0.95 (C10-$C\underline{H}_3$), 0.6 (C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).



(CXV)

Characterization of the compound, m.p. 187° as 5,6β-epoxy-4,4-dimethyl-5β-cholestan-3-one (CXVI)

The compound m.p. 187°, the isomer of (CXV) showed molecular composition $C_{29}H_{48}O_2$. The I.R. spectrum exhibited bands at 1700 and 805 cm^{-1} for carbonyl and epoxide respectively. A multiplet appeared at δ 3.06 integrating for one proton is ascribable to C6-$\underline{H}$, no signals in downfield region were observed in the N.M.R. spectrum of the (CXVI). The other signals were seen at δ 1.2 (C10-$C\underline{H}_3$), 0.65 (C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).



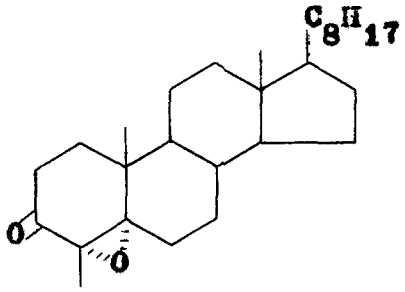
(CXVI)

Baeyer-Villiger oxidation of 4-methylcholest-4-en-3-one (CII)

The ketone (CII) was treated with perbenzoic acid (1.1 mole equivalent) in the presence of p-toluenesulphonic acid as catalyst. The reaction mixture after usual work up and column chromatography over silica gel provided compounds, m.p. 125° and 130°.

Characterization of the compound, m.p. 125° as 4α,5-epoxy-4β-methyl-5α-cholestan-3-one (CXVI)

The compound, m.p. 125° was analysed for $C_{28}H_{46}O_2$. I.R. spectrum showed peaks at 1700 and 740 cm^{-1} for carbonyl and epoxide respectively. The N.M.R. spectrum was found featureless. Methyl signals were appeared at δ 1.37s (C4-βCH_3), 1.0 (C10-CH_3), 0.66 (C13-CH_3), 0.9 and 0.8 (remaining methyl protons).

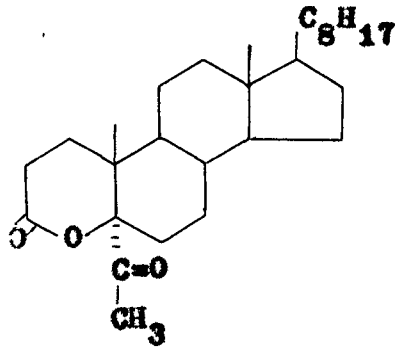


(CXVII)

Characterization of the compound, m.p. 158° as 5-acetyl-4-oxa-5α-cholestan-3-one (CXVIII)

The compound, m.p. 158° was analysed correctly for $C_{28}H_{46}O_3$ and this composition was supported by mass spectrum showing molecular ion peak at m/e 430 . I.R. spectrum showed a characteristic peaks at 1710 (C=O) and 1760 cm^{-1} (δ-lactone). In N.M.R. spectrum a singlet at δ 2.17 integrating for three protons was ascribable to C5-CO-CH_3 . Other

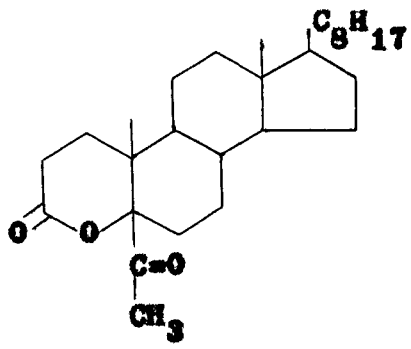
signals were exhibited at δ 1.0 (C10-CH_3), 0.67 (C13-CH_3), 0.91 and 0.81 (remaining methyl protons).



(CXVIII)

Characterization of the compound m.p. 120° as 5-acetyl-4-oxa-5β-cholestan-3-one (CXIX)

The compound, m.p. 120° was shown to be an isomer of the compound (CXVIII) by its analysis ($C_{28}H_{46}O_3$) and the molecular ion peak (m/e 430) in its mass spectrum. I.R. spectrum exhibited bands at 1705 (C=O), 1725 (δ-lactone). N.M.R. spectrum was almost clean, only methyl signals were seen at δ 2.18 (C5-$COCH_3$), 1.05 (C10-CH_3), 0.67 (C13-CH_3), 0.91 and 0.81 (remaining methyl protons).



(CXIX)

This reaction showed results similar from the earlier observation[25]. The only difference is that we obtained three compounds (CXVII-CXIX) directly from (CII), but earlier observation results only two compounds, m.p. 125° and 158° (CXVII and CXVIII). The compound m.p. 120° (CXIX) was reported indirectly, but all the three compounds were found similar in all respects to the authentic samples.

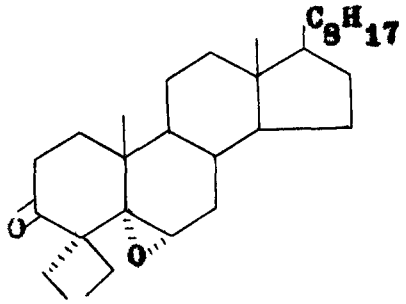
Baeyer-Villiger oxidation of 4,4-diethylcholest-5-en-3-one (CIII)

The ketone (CIII) was treated with perbenzoic acid (1.1 mole equivalent) in the similar fashion. After usual work up and column chromatography over silica gel a compound, m.p. 84° was obtained.

Characterisation of the compound, m.p. 84° as 5,6α-epoxy-4,4-diethyl-5α-cholestan-3-one (CXX)

The compound, m.p. 84° was analysed for $C_{31}H_{52}O_2$. This molecular composition suggested the addition of an oxygen atom to the parent ketone (CIII). The I.R. spectrum showed bands at 1710 (C=O) and 875 cm^{-1} (epoxide). In N.M.R. spectrum a doublet at δ 2.91 (J_{ae} = 5 Hz) integrating for one proton is ascribable for C6-β<u>H</u>. Since C6-<u>H</u> appeared as doublet, it means C6-<u>H</u> is axially oriented, because the dihedral angle between C6-H and one C7-proton is ~90°, so it does not split.

The other signals were exhibited at δ 0.95 (C10-C$\underline{H}_3$), 0.65 (C13-C$\underline{H}_3$), 0.82 and 0.70 (remaining methyl protons).



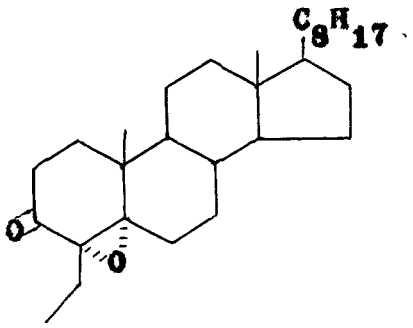
(CXX)

Baeyer-Villiger oxidation of 4-ethylcholest-4-en-3-one (CIV)

The ketone (CIV) on usual treatment with perbenzoic acid and column chromatography over silica gel provided two compounds, m.p. 96° and 112°.

Characterisation of the compound, m.p. 96° as 4α,5-epoxy-4β-ethyl-5α-cholestan-3-one (CXXI)

The compound, m.p. 96° was analysed for $C_{29}H_{48}O_2$. The I.R. spectrum showed peaks at 1700 and 790 cm^{-1} which are characteristic to carbonyl and epoxide respectively. The N.M.R. spectrum showed the signals at δ 1.0 (C10-C$\underline{H}_3$), 0.68 (C13-C$\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons). The epoxide has been shown to be an α-oriented on the mechanistic ground[32] as well as previous observation[33].

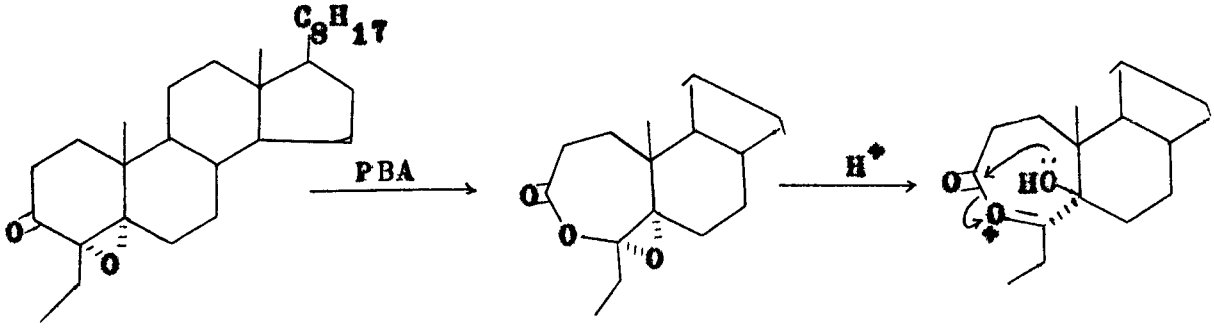


(CXXI)

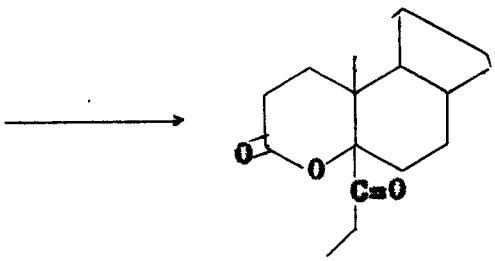
Characterization of the compound, m.p. 112° as 5-propanyl-4-oxa-5β-cholestan-3-one (CXXII)

The compound, m.p. 112° showed the molecular composition $C_{29}H_{48}O_3$. Analysis showed the addition of two oxygen atoms to (CIV). I.R. spectrum exhibited bands at 1700 (C=O) and 1750 cm^{-1} (δ-lactone carbonyl). N.M.R. spectrum of (CXXII) displayed a multiplet centred at δ 2.4 integrating for 4 protons which were ascribed to α-methylene protons. The other signals were seen at δ 1.0 (C10-CH_3), 0.66 (C13-CH_3), 0.9 and 0.8 (remaining methyl protons).

The propanyl derivative in (CXXII) may be due to the acid catalysed rearrangement of the intermediate (CXXI-a) (Scheme - 19). Such type of intermediate was also suggested by Pinhey and Schaffner[25]. The structure (CXXII) was further substantiated by conversion of CXXI to CXXII on treatment with perbenzoic acid under similar conditions.



(CXXI) (CXXI-a)



(CXXII)

Scheme - 19

EXPERIMENTAL

All melting points are uncorrected. I.R. spectra were determined in Nujol with Perkin-Elmer 237 Spectrophotometer. N.M.R. spectra were run in $CDCl_3$ on a Varian A60 instrument with Me_4Si as the internal standard. U.V. spectra were obtained in methanol with a Beckman DK2 Spectrophotometer. T.L.C. plates were coated with silica gel. A 20% aqueous solution of perchloric acid was used as spraying agent. Light petroleum refers to a fraction of b.p. 60-80°. N.M.R. values are given in ppm (s = singlet, d=doublet, t=triplet, br=broad, mc=multiplet centred at).

3β,5,6β-Trihydroxy-5α-cholestane

A mixture of cholesterol (20 g) and formic acid (28 ml; 98%) was heated on a water bath at 70-80° for 5 min and then allowed to attain room temperature. Hydrogen peroxide (20 ml, 30%) was added to the mixture and it was kept at room temperature for 12 hrs with occasional shaking. Boiling water(ca 300 ml) was added with stirring and the reaction mixture was allowed to attain room temperature when a white grannular solid separated which was filtered under suction and air dried. The solid was dissolved in methanol (600 ml) and the solution heated with sodium hydroxide solution (20 ml; 25%) for 10 min on steam bath.

It was acidified with hydrochloric acid and diluted with boiling water (300 ml). The triol obtained on cooling was collected by filtration under reduced pressure and recrystallized from methanol (18 g), m.p. 237-239° (reported[34] m.p. 237-239°).

5-Hydroxy-3,6-diacetoxy-5α-cholestane

The triol (50 g) dissolved in pyridine (150 ml) and added acetic anhydride (100 ml) was heated on a water bath for 3 hrs. The resulting solution was poured into crushed ice water mixture with stirring. A solid was obtained, which was filtered under suction, washed with water until free from pyridine and air dried. The crude product was recrystallized from methanol (45 g), m.p. 165-166° (reported[35] m.p. 166°).

3,6β-Diacetoxy-19-nor-5-methyl-5β-cholest-9(10)-ene

A mixture of 5-hydroxy-3,6-diacetoxy-5α-cholestane (10 g) potassium hydrogen sulphate (40 g) and acetic anhydride (300 ml) was heated on a steam bath for 2 hrs. The resulting solution was poured into water. A solid was obtained, which was filtered under suction, washed with water. The crude product was recrystallized from aqueous acetone (4.5 g), m.p. 127-128° (reported[35] m.p. 128°).

3,6β-Dihydroxy-19-nor-5-methyl-5β-cholest-9(10)-ene

A mixture of 3,6β-diacetoxy-19-nor-5-methyl-5β-cholest-9(10)-ene (4 g) and methanolic potassium hydroxide (300 ml, 5%) was refluxed on a water bath for 2 hrs. The resulting solution was poured into ice cold water. The reaction mixture was acidified with HCl and worked up in the usual manner. The solvent was evaporated, and residue obtained was crystallized from methanol (3.5 g), m.p. 84-86° (reported[35] m.p. 82-90°).

5-Methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (XCIX)

The diol (4 g) was dissolved in acetone (250 ml) and was cooled at 0-5°. After stirring for 5 min Jones' reagent was added with stirring till a brown colour persisted. The mixture was allowed to remain at this temperature for 30 min. Water (200ml) was added and reaction mixture was worked up with ether. The ethereal solution was washed with water and dried over sodium sulphate (anhydrous). The solvent was evaporated to yield an oil. Crystallization from acetone-methanol gave the diketone (XCIX)(2 g), m.p. 102-104° (reported[35] m.p. 104-106°).

The Baeyer-Villiger oxidation of 5-methyl-19-nor-5β-cholest-9(10)-ene-3,6-dione (XCIX):5-Methyl-19-nor-9α,10α-epoxy-5-cholestane-3,6-dione (CV), 5-methyl-19-nor-10α-hydroxyl-5β-cholest-8(9)-ene-3,6-dione (CVI), 5-methyl-19-nor-9β,10α-dihydroxy-3,4,5,6-disecocholest-6-oic acid 6,9-lactone (CVII), 19-nor-3-oxa-4-keto-5a-methyl-9β,10α-dihydroxy-5,6-seco-A-homocholest-5-en-6-oic acid 6,9-lactone (CVIII) and 19-nor-4,6-dioxa-3,5,6a-triketo-5a-methyl-10α-hydroxy-A,B-bishomo-cholest-8(9)-ene (CIX)

To a solution of (XCIX)(3 g) in chloroform (20 ml) were added a freshly prepared chloroform solution of perbenzoic acid (2.5 mole equivalent) and a few crystals of p-toluenesulphonic acid monohydrate (as catalyst). The reaction mixture was allowed to stand at room temperature for three days. The solvent was removed under reduced pressure. The residue was extracted with ether and the ethereal solution washed with sodium bicarbonate solution (5%), water and dried over sodium sulphate (anhydrous). On removal of the solvent, the crude product (ca ~ 2.9 g) was chromatographed over silica gel. Elution with light petroleum: ether (4:1) gave (CV)(0.75 g), m.p. 133° (reported[30] m.p. 131-32°). Further elution with light petroleum:ether (3:1) gave a solid (CVI) which was recrystallized from light petroleum (0.6 g), m.p. 175°.

Analysis. Found: C, 78.35; H, 10.02

$C_{27}H_{42}O_3$ requires: C, 78.25; H, 10.14%.

I.R. ν max. 3400 (OH), 1700 and 1725 cm^{-1} (carbonyls).

N.M.R. δ 2.55m (α-methylene protons), 105 (C5-C$\underline{H}_3$), 0.7(C13-C$\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons).

Elution with light petroleum:ether (1:1) afforded a non-crystallizable oil (CVII)(Ca 0.3 g).

Analysis. Found: C, 67.43; H, 9.24.

$C_{27}H_{44}O_7$ requires: C, 67.50; H, 9.16%.

I.R. ν max. 3650 (OH), 3420 (C$\underline{O}$OH), 1785 (γ-lactone), 1720 cm^{-1} (C$\underline{O}$OH).

N.M.R. δ 7.45m (C3 and C4-COO$\underline{H}$), 2.65 (α-methylene protons), 0.93 and 0.83 (methyl protons).

Continued elution with light petroleum:ether (1:1) yielded a solid compound (CVIII)(0.25 g) which was recrystallized from light petroleum, m.p. 178°.

Analysis. Found: C, 72.58; H, 9.62.

$C_{27}H_{42}O_5$ requires: C, 72.64; H, 9.41%.

I.R. ν max 3418 (OH), 1770 (γ-lactone), 1695 cm^{-1} (C=C-C$\underline{H}$-).

N.M.R. δ 5.2 (C4a-$\underline{H}$), 4.0 sc ($C2H_2$-O-), 2.56 (C5a-C$\underline{H}_3$), 0.68 (C13-C$\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons).

Further elution with ether provided another solid (CIX) which was recrystallised from light petroleum (0.30 g), m.p. 170°.

Analysis. Found: C, 70.35; H, 8.54.

$C_{27}H_{40}O_6$ requires: C, 70.43; H, 8.69%.

I.R. ν max. 3330 (OH), 1785, 1750 (acid anhydride), 1705 cm^{-1} (ϵ-lactone).

N.M.R. δ 3.2m (4H, C2-$\underline{H}_2$; C7-$\underline{H}_2$), 1.0 (C5-$\underline{CH}_3$), 0.7 (C13-$\underline{CH}_3$), 0.9 and 0.8 (remaining methyl protons).

Base hydrolysis of (CIX): 19-Nor-5-methyl-5-hydroxy-3,4,5,6-disecocholest-7(8), 9(10)-dien-2,5,7-tricarboxylic acid (CX)

A solution of (CIX)(0.25 g) in methanolic sodium hydroxide (50 ml; 5%) was heated under reflux for 1 hr. The reaction mixture was poured into an excess of water and carefully acidified with HCl, extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate (anhydrous). After removal of the solvent a non-crystallizable oil (CX)(0.17 g) was obtained.

Analysis. Found: C, 67.90; H, 8.54.

$C_{27}H_{42}O_7$ requires: C, 67.79; H, 8.73%.

I.R. ν max. 3650 (OH), 3400 (COO$\underline{H}$), 1710 ($\underline{C}$OOH), 1650 (C=C-C=C-$\underline{C}$O-OH) and 1620 cm^{-1} (C=C).

N.M.R. δ 6.7m (C3-$\underline{C}$OOH, C5-$\underline{C}$OOH, C5-O$\underline{H}$ and C7-$\underline{H}$), 1.26 (C5-$\underline{CH}_3$), 0.9 and 0.8 (remaining methyl protons),

3β-Chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100 g) at room temperature. A vigorous

reaction ensued with the evolution of gaseous products. When the reaction slackened the mixture was gently heated for a temperature 50-60° on a water bath for 1 hr and then poured onto crushed ice water with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice cooled water and air dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (95.5 g), m.p. 95-96° (reported[36] m.p. 96-97°). It gave positive Beilstein Test and yellow colour with tetranitromethane in chloroform.

3β-Chloro-5,6β-dihydroxy-5α-cholestane

Cholesteryl chloride (28 g) in hot acetic acid (600 ml) was treated with hydrogen peroxide (12 ml; 30%) and the reaction mixture was heated at 95° for 30 min. Removal of the solvent in vacuum gave an oily product which was extracted with ether. Evaporation of the solvent provided an oil (ca 29 g) which was chromatographed on alumina oxide (600 g). Elution with benzene: pentane (3:7) gave unreacted cholesteryl chloride (3.3 g). Elution with ether gave (15 g) of 3β-chloro-5,6β-dihydroxy-5α-cholestane which was crystallized from ether:pentane, m.p. 126° (reported[37] m.p. 126°).

3β-Chloro-6β-acetoxy-5α-hydroxycholestane

3β-Chloro-5,6β-dihydroxy-5α-cholestane (50 g) was refluxed in pyridine (75 ml) (freshly distilled over KOH) and acetic anhydride (50 ml) for 2 hrs. The resulting

solution was poured into crushed ice water mixture with stirring. A solid thus obtained was filtered under suction, washed with water (until free from pyridine) and air dried. The crude product on recrystallization from methanol gave the pure compound (45 g), m.p. 138-140°.

3β-Chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6 -acetate

A mixture of 3β-chloro-6β-acetoxy-5α-hydroxycholestane (10 g), potassium hydrogen sulphate (40 g) and acetic anhydride (100 ml) was refluxed over a period of 1 hr. The resulting solution was poured into water and worked up in the usual manner. On evaporation of the solvent the residue was obtained which was chromatographed over silica gel. The solid thus obtained, on recrystallization gave pure compound (5 g), m.p. 87-89° (reported[38] m.p. 87-88°).

3β-Chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (C)

A mixture of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6β-acetate (5 g) and methanolic potassium hydroxide (350 ml; 5%) was refluxed on steam bath for 2 hrs. The resultant mixture was poured into ice cold water, acidified with dCl. The reaction mixture was worked up in the usual manner as described earlier. The solvent was evaporated. The residue thus obtained was dissolved in acetone (250 ml) and the solution was cooled 0-5°.

Jones' reagent was gradually added with stirring till brown colour persisted. The mixture was then allowed to remain at this temperature for 30 min. Water (200 ml) was added to it and extracted with ether. Evaporation of the solvent gave a residue which on crystallization from light petroleum gave the compound (C) (2.5 g), m.p. 63-64°.

Analysis. Found: C, 77.32; H, 10.24.

$C_{27}H_{43}OCl$ requires: C, 77.51; H, 10.28%.

I.R. νmax 1720 (C=O), 745 cm^{-1} (C-Cl).

N.M.R. δ 4.41m (C3-αH), 1.42 (C5-CH_3), 0.78 (C13-CH_3), 0.9 and 0.8 (remaining methyl protons).

<u>The Baeyer-Villiger oxidation of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (C):3β-Chloro-5-methyl-19-nor-5β-cholestan-9α,10α-epoxy-6-one (CXI) and 3β-chloro-19-nor-6-oxa-5α-methyl-9α,10α-epoxy-8-homocholestan-7-one (CXII)</u>

A solution of (C)(2 g) in chloroform (20 ml) was treated with perbenzoic acid (2.5 mole equivalent) in the manner described earlier. After the usual work up of the reaction mixture, residue thus obtained was chromatographed over a column of silica gel. Elution with light petroleum ether (17:1) gave (CXI) which was recrystallized from light petroleum (0.75 g), m.p. 138°.

Analysis. Found: C, 74.51; H, 10.12.

$C_{27}H_{43}O_2Cl$ requires: C, 74.65; H, 9.90%.

I.R. ν max 1695 (C=O), 900 (epoxide), 715 cm^{-1} (C-Cl).

N.M.R. δ 4.6m (C3-$\underline{H}$), 1.36 (C5-$C\underline{H}_3$), 0.75 (C13-$C\underline{H}_3$), 0.98 and 0.90 (remaining methyl protons).

Further elution with light petroleum:ether (16:1) afforded a solid which on recrystallization from light petroleum gave (CXII)(0.5 g) m.p. 105°.

Analysis. Found: C, 72.20; H, 0.43.

$C_{27}H_{43}O_3Cl$ requires: C, 72.00; H, 9.55%.

I.R. ν max 1705 (ϵ-lactone), 895 (epoxide), 705 cm^{-1} (C-Cl).

N.M.R. δ 3.7m (C3-$\underline{H}$; $W\frac{1}{2}$ = 6 Hz), 2.35 (C7a-$\underline{H}_2$), 1.35 (C5- $C\underline{H}_3$), 0.73 (C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

3β-Hydroxy-5,6β-dibromo-5α-cholestane

To a solution of cholesterol (14 g) in ether (100 ml) was added gradually the bromine solution (9.6 g in 100 ml of glacial acetic acid containing 1 g of anhydrous sodium acetate). The solid thus obtained was filtered under suction and washed with cold ether-acetic acid mixture (3:7). The dried dibromide (16 g) showed m.p. 113-114° (reported[39] m.p. 114°).

5,6β-Dibromo-5α-cholestan-3-one

3β-Hydroxy-5,6β-dibromo-5α-cholestane (10 g) was suspended in acetone (300 ml). The suspension was cooled to 0-5°. It was stirred for 5 min and to this mixture Jones' reagent was

added dropwise over a period of 20 min at the maintained temperature of 0-5°. Water (200 ml) was added and dibromoketone was filtered under suction, washed with water, methanol and air dried (9 g), m.p. 73-75° (reported[39] m.p. 73-75°).

Cholest-5-en-3-one

To a solution of 5,6β-dibromo-5α-cholestan-3-one (5 g) in ether (100 ml) was added glacial acetic acid (2.3 ml). Zinc dust (7.5 g) was added in small portions during 30 min with continuous shaking. After complete addition, the ethereal solution containing zinc dust was filtered, washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate (anhydrous). Removal of the solvents provided an oil which was crystallized from methanol (3.3 g) m.p. 126-27° (reported[39] m.p. 129°).

Cholest-4-en-3-one

Cholest-5-en-3-one (4 g) was dissolved in ethanol (40 ml) and to this was added a solution of oxalic acid (0.5 g) in ethanol (5 ml). The reaction mixture was refluxed for 15 min, then allowed to stand at room temperature. Crystallisation occurs after 1 hr and to ensure complete crystallization, it was cooled at 0-4° and then filtered. The crude product was recrystallized from methanol to give the ketone (3 g) m.p. 80° (reported[39] m.p. 81-82°).

Reaction of cholest-4-en-3-one with methyl iodide: 4,4-Dimethylcholest-5-en-3-one (CI) and 4-methylcholest-4-en-3-one (CII)

Potassium (0.3 g)(3 mole equivalent) was dissolved in dry t-butyl alcohol (10 ml) and the resultant solution was added to a boiling solution of cholest-4-en-3-one (10g) in benzene (30 ml). Methyl iodide (3 ml) in benzene (30 ml) was then added dropwise and refluxing was continued for 25 min. The solution was allowed to cool down, water (5 ml) was added to this and the solvent was evaporated to dryness under reduced pressure. The dried mass was taken in ether and the insoluble potassium iodide was separated on filteration. The ethereal layer was washed with water, and dried over sodium sulphate (anhydrous). An oil was obtained on evaporation of the solvent which was chromatographed over a column of silica gel (150 g). Elution with light petroleum yielded (CI)(2 g) which was crystallized from methanol m.p. 173° (reported[40] m.p. 172-74°). Further elution with light petroleum:benzene (9:1) gave solid (CII), recrystallized from light petroleum (1 g), m.p. 100° (reported[40] m.p. 101-103°).

The Baeyer-Villiger oxidation of 4,4-dimethylcholest-5-en-3-one (CI):5,6α-Epoxy-4,4-dimethyl-5α-cholestan-3-one (CXV) and 5,6β-epoxy-4,4-dimethyl-5β-cholestan-3-one (CXVI)

The ketone (CI)(1 g) was treated with perbenzoic acid (1:1 molo equivalent) and a few crystals of p-toluenesulphonic acid was added as a catalyst. The reaction mixture was allowed to stand at room temperature for 3 days. The reaction mixture was taken in ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate (anhydrous). The residue obtained on evaporation of the solvent was chromatographed over silica gel. Elution with light petroleum:ether (25:1) provided a solid (CXV)(0.15 g) which was recrystallized from light petroleum, m.p. 144°.

Analysis. Found: C, 81.61; H, 11.28.

$C_{29}H_{48}O_2$ requires: C, 81.32; H, 11.21%.

I.R. ν max. 1710 (C=O), 720 cm^{-1} (epoxide).

N.M.R. δ 2.93d (C6-$\beta\underline{H}$; $J_{a,e}$ = 5 Hz), 0.95 (C10-$C\underline{H}_3$), 0.6(C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

Further elution with light petroleum:ether (24:1) gave (CXVI)(0.15 g) as fine crystals on recrystallization from light petroleum, m.p. 187°.

Analysis. Found: C, 79.9; H, 11.19.

$C_{29}H_{48}O_2$ requires: C, 81.3; H, 11.21%.

I.R. max 1700 (C=O), 905 cm^{-1} (epoxide).

N.M.R. 3.06m (C6-α-H), 2.4 (α-methylene protons), 1.2 (C10-CH_3), 0.65 (C13-CH_3), 0.91 and 0.81 (remaining methyl protons).

The Baeyer-Villiger oxidation of 4-methylcholest-4-en-3-one (CII): 4α,5-Epoxy-4β-methyl-5α-cholestan-3-one (CXVII), 5-acetyl-4-oxa-5α-cholestan-3-one (CXVIII) and 5-acetyl-4-oxa-3β-cholestan-3-one (CXIX)

The ketone (CII)(1 g) was treated with perbenzoic acid (1.1 mole equivalent) in the usual manner. The reaction mixture after work up was chromatographed over silica gel. Elution with light petroleum:ether (19:1) yielded (CXVII)(0.2 g), which was crystallized from light petroleum, m.p. 125-26°.

Analysis. Found: C, 80.8; H, 11.21.

$C_{29}H_{46}O_2$ requires: C, 81.1; H, 11.20%.

I.R. ν max 1700 (C=O), 740 cm^{-1} (epoxide).

N.M.R. δ 1.37s (C4a-CH_3), 1.0 (C10-CH_3), 0.66 (C13-CH_3), 0.9 and 0.8 (remaining methyl protons).

Elution with light petroleum:ether (10:1) gave a solid (CXVIII) which was recrystallized from light petroleum (0.13 g) m.p. 158°.

Analysis. Found: C, 78.2; H, 10.7.

$C_{29}H_{46}O_3$ requires : C, 78.1; H, 10.8%.

I.R. ν max 1710 (C=O), 1760 cm^{-1} (δ-lactone).

N.M.R. δ 2.17 ($C5-COC\underline{H}_3$), 1.0 ($C10-C\underline{H}_3$), 0.67 ($C13-C\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons).

Further elution with light petroleum:ether (9:1) afforded (CXIX) (0.07 g), recrystallized from light petroleum as fine crystals m.p. 120°.

Analysis. Found: C, 78.2; H, 10.7.

$C_{29}H_{46}O_3$ requires: C, 78.1; H, 10.3%.

I.R. ν max 1705 (C=O), 1725 cm^{-1} (δ-lactone).

N.M.R. δ 2.13 ($C5-COC\underline{H}_3$), 1.05 ($C10-C\underline{H}_3$), 0.67 ($C13-C\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons).

Reaction of cholest-4-en-3-one with ethyl iodide:4,4-Diethylcholest-5-en-3-one (CIII) and 4-ethylcholest-4-en-3-one(CIV)

A solution of potassium (3.3 g) in dry t-butyl alcohol was added to a boiling solution of cholest-4-en-3-one (10 g) in t-butyl alcohol (250 ml). It was heated under reflux for 15 min. To this solution was added dropwise a solution of ethyl iodide (2.5 ml) in dry t-butyl alcohol (50 ml) over a period of 2 hrs. The reaction mixture was refluxed for an additional 30 min. Solvent was evaporated to dryness under reduced pressure. Usual workup gave an oil which was chromatographed over a column of silica gel. Elution with light petroleum: benzene (16:1) gave (CIII) (1.71 g) m.p. 96° (reported[41] m.p. 96-97°). Further elution with light petroleum:benzene (10:1) furnished (CIV)(2.5 g), recrystallized from light petroleum m.p. 84° (reported[41] m.p. 84-86°).

The Baeyer-Villiger oxidation of 4,4-diethylcholest-5-en-3-one (CIII): 5,6α-Epoxy-4,4-diethyl-5α-cholestan-3-one (CXX)

To a solution of (CIII)(1 g) in chloroform (12 ml) was added a chloroform solution of perbenzoic acid (1.1 mole equivalent) and a few crystals of p-toluenesulphonic acid as a catalyst. The reaction mixture was allowed to stand at room temperature for 2 days. After usual work up of the reaction mixture, the residue obtained was chromatographed over silica gel (20 g). Elution with light petroleum:ether (25:1) provided 5,6α-epoxy-4,4-diethyl-5α-cholestan-3-one (CXX)(0.25 g), recrystallized from light petroleum, m.p. 84°, . . .

Analysis. Found: C, 81.70; H, 11.40.

$C_{31}H_{52}O_2$ requires: C, 81.57; H, 11.40%.

I.R. ν max 1710 (C=O), 875 cm^{-1} (epoxide).

N.M.R. δ 2.91d (C6-$\beta\underline{H}$; J_{ae} = 5 Hz), 0.93 (C10-$C\underline{H}_3$), 0.65(C13-$C\underline{H}_3$), 0.92 and 0.70 (remaining methyl protons).

The Baeyer-Villiger oxidation of 4-ethylcholest-4-en-3-one (CIV): 4α,5-Epoxy-4β-ethyl-5α-cholestan-3-one (CXXI) and 5-propanyl-4-oxa-5β-cholestan-3-one (CXXII)

The ketone (CIV)(1 g) was treated with perbenzoic acid (1.1 mole equivalent) in the presence of p-toluenesulphonic acid (in catalytic amount). Usual work up of the reaction mixture, the residue obtained was chromatographed over silica gel (20 g). Elution with light petroleum:ether (20:1) provided (CXXI)(0.2 g)

which was recrystallized from light petroleum, m.p. 96°.

Analysis. Found: C, 81.70; H, 10.95.

$C_{29}H_{48}O_2$ requires: C, 81.32; H, 11.21%.

I.R. ν max 1700 (C=O), 790 cm^{-1} (epoxide).

N.M.R. δ 1.0 (C10-$\underline{CH}_3$), 0.68 (C13-$\underline{CH}_3$), 0.9 and 0.8 (remaining methyl protons).

Further elution with light petroleum:ether (17:1) gave ketone (CIV)(0.03 g) m.p. and m.m.p. 84°. Continued elution with light petroleum:ether (13:1) gave a solid which was recrystallized from light petroleum as a fine crystals (CXXII) (0.15 g), m.p. 112°.

Analysis. Found: C, 77.98; H, 10.66.

$C_{29}H_{48}O_3$ requires: C, 78.40; H, 10.80%.

I.R. ν max 1710 (C=O), 1750 cm^{-1} (δ-lactone).

N.M.R. δ 3.4 mc (4H, α-methylene protons), 1.0 (C10-$\underline{CH}_3$), 0.66 (C13-$\underline{CH}_3$), 0.9 and 0.8 (remaining methyl protons).

The mass spectra were measured in a Varian MAT-311(A) mass spectrometer at 70eV using a direct insertion technique at source temperature of about 160°C.

The value (m/e) of the fragment ions from various compounds are tabulated below. The value in percentage are the relative abundance (%) of the peaks with respect to base peak as 100%, and the composition of fragment ions as determined by accurate mass measurement.

5-Methyl-10-nor-10α-hydroxy-5β-cholest-8(9)-ene-3,6-dione (CVI)

$M^{+\cdot}$ 414 (10%; $C_{27}H_{42}O_3$), m/e 399(4.16), 397(6.25), 396(19.27), 386(5.20), 381(7.29), 372(7.29), 359(4.16), 355 (4.16), 354(6.25), 345(10.42), 344(10.42), 341(6.25), 331(11.46), 330(20.31), 329(9.37), 316(11.46), 301(10.42), 283(7.29), 255 (5.20), 247(7.29), 241(10.42), 229(5.20), 219(4.16), 217(17.70), 215(5.20), 213(5.20), 207(6.25), 205(5.20), 203(5.20), 201(5.70), 199(6.77), 193(14.58), 191(10.37), 189(9.33), 187(7.29), 177 (5.29), 175(7.29), 173(6.25), 171(7.29), 163(6.25), 161(8.33), 159(9.38), 157(8.95), 149(8.33), 147(13.54), 145(10.42), 143 (7.29), 137(6.25), 135(9.33), 134(7.29), 133(12.50), 131(10.42), 123(10.42), 121(12.50), 119(11.46), 117(6.25), 110(5.20), 109(15.60), 107(15.60), 105(19.79), 97(9.37), 95(25.0), 93(14.58), 91(12.50), 83(6.25), 81(28.12), 79(10.42), 71(14.58), 69(25.0), 67(12.50), 57(31.25), 55(31.25), 43(55.83).

19-Nor-3-oxa-4-keto-5a-methyl-9β,10α-dihydroxy-5,6-seco-A-homocholest-5-en-6-oic acid 6,9-lactone (CVIII)

$M^{+\cdot}$ 446 (1.04; $C_{27}H_{42}O_5$), m/e 401 (19.79), 400 (46.87), 389 (13.54), 385 (9.33), 382 (5.73), 372 (20.83), 371 (15.62), 370 (6.77), 359 (11.46), 357 (7.29), 354 (4.16), 343 (4.16), 341 (4.16), 329 (6.25), 327 (11.45), 315 (4.16), 306 (21.87), 305 (100), 297 (9.33), 275 (4.16), 269 (7.29), 265 (7.81), 263 (7.29), 259 (15.62), 247 (7.29), 245(17.70), 241 (8.33), 232 (8.33), 231(6.77), 227(12.5), 215(8.33), 207(11.45), 206 (19.75), 205(13.50), 204(13.54), 201(10.42), 199(9.89), 195(5.21), 193(13.54), 191(13.02), 190(9.37), 189(19.79), 187(12.5), 185 (14.06), 181(10.41), 180(9.37), 177(8.35), 176(18.75), 163(18.75), 161(14.06), 159(15.62), 157(10.42), 153(9.37), 152(9.37), 151 (11.46), 149(14.58), 147(23.43), 145(13.54), 143(8.85), 141(21.87), 139(10.42), 137(13.54), 135(20.83), 133(20.83), 131(11.46), 124(11.45), 123 (23.43), 122(11.45), 121(18.22), 119(15.62), 109(26.66), 107(29.16), 105(16.66), 99(13.54), 97(17.70), 95 (46.87), 93(27.08), 91(17.70), 83(22.91), 81(30.20), 71(30.72), 69(43.77), 66(22.91), 57(59.37), 55(33.33).

19-Nor-4,6-dioxa-3,5,6a-triketo-5a-methyl-10α-hydroxy-A,B-bishomocholest-8(9)-ene (CIX)

$M^{+\cdot}$ 460 (0.52; $C_{27}H_{40}O_6$), m/e 419 (22.91), 418 (80.72), 401(28.12), 400(100), 390(6.25), 388(4.16), 385(8.33), 372(4.16), 359(9.37), 358(32.29), 345(14.58), 328(7.81), 327(30.72),

317(7.29), 306(10.42), 305(53.12), 304(7.29), 301(4.16), 287 (13.05), 277(7.29), 264(18.75), 263(80.72), 259(6.77), 246(6.25), 245(19.79), 233(7.29), 232(7.81), 227(10.42), 223(6.25), 222 (32.29), 204(20.31), 201(6.77), 199(5.20), 193(11.45), 191(12.5), 187(12.5), 185(10.42), 173(14.50), 161(7.29), 156(7.81), 155 (32.19), 151(11.97), 149(6.25), 147(11.97), 145(6.25), 137(6.25), 133(8.33), 125(7.29), 123(8.33), 121(11.46), 119(6.77), 113 (7.29), 110(13.05), 103(10.42), 93(8.33), 96(17.70), 94(11.46), 84(11.46), 82(15.62), 69(14.58), 51(18.75).

3β-Chloro-19-nor-6-oxa-5α-methyl-9α,10α-epoxy-β-homocholestan 7-one (CXII)

$M^{+\cdot}$ 450/452 (1.04; $C_{27}H_{43}O_3Cl$), m/e 415(5.20), 414(18.66), 396(5.20), 387(12.50), 386(40.87), 372(3.64), 371(4.16), 357 (5.20), 348(8.33), 329(4.16), 306(17.70), 303(79.68), 304(11.46), 301(5.20), 291(4.16), 283(4.16), 277(6.75), 264(7.29), 263 (35.42), 247(8.33), 245(8.83), 241(5.20), 231(6.75), 219(6.25), 207(6.25), 205(6.25), 203(8.33), 193(12.50), 191(28.12), 190 (9.37), 189(6.75), 179(9.37), 177(11.96), 175(8.83), 173(7.29), 166(8.33), 165(22.91), 164(67.71), 163(11.46), 161(11.46), 159(9.37), 157(8.33), 152(8.33), 151(30.20), 149(19.79), 148 (19.79), 147(81.45), 146(13.54), 145(10.42), 138(13.54), 137 (39.58), 135(26.04), 134(22.91), 133(40.62), 131(11.46), 124 (14.58), 123 (25.00), 122(21.87), 121(34.37), 119(20.83), 111(14.58), 110(23.43), 109(100), 108(20.83), 107(40.62), 105(23.95), 97(21.87), 96(14.58), 95(56.25), 93(44.71), 91(18.22), 83(34.89), 81(63.54), 79(27.08), 71(41.66), 69(54.16), 67(24.48), 57(90.21).

REFERENCES

1. A. Baeyer and V. Villiger, Ber., 32, 3625 (1899).

2. C.H. Hassall, "Organic Reactions", IX, p. 73 (John Wiley and Sons, New York)(1957).

3. J.A. Gardner and W. Godden, Biochem. J., 7, 588 (1913).

4. G.W. Ellis and J.A. Gardner, ibid., 12, 72 (1918).

5. J.E. Bolliger and J.L. Courtney, Aust. J. Chem., 17,440(1964).

6. D. Rosenthal, L.O. Wiedermeyer and J. Fried, J. Org. Chem., 30, 510 (1965).

7. S. Hara, Chem. Pharm. Bull. (Japan), 12, 1531 (1964).

8. M.S. Ahmad, M. Asif and M. Mushfiq, Ind. J. Chem., 16B, 426 (1978).

9. P. Bladon and W. McLeakin, J. Chem. Soc., 3504 (1961).

10. A. Lardon, J. Schmidlin, A. Wettstein and T. Reichstein, Helv. Chim. Acta., 40, 662 (1957).

11. S.N. Suryawanshi and U.R. Nayak, Ind. J. Chem., 18B,106(1979).

12. M.S. Ahmad, G. Moinuddin and Israr A. Khan,J. Org. Chem., 43, 163 (1978).

13. G.F. Fonken and H.M. Miles, J. Org. Chem., 28, 2432 (1963).

14. M.S. Ahmad, Shafiullah, M. Mushfiq and (in part) M. Asif, Ind. J. Chem., 8, 1062 (1970).

15. N. Pritejaeff, Bull. Soc. Chim. (France), 41, 687 (1927).

16. J. Boeseken and A.L. Soesman, Rec. Trav. Chim., 52, 874 (1933).

17. H.M. Walton, J. Org. Chem., 22, 1161 (1957).

18. G.B. Payne and P.H. Williams, J. Org. Chem., 24, 284 (1959).

19. E. Caspi, Y.W. Chang and R.I. Dorfman, J. Med. Pharm. Chem., 5, 714 (1962).

20. A. Salaman, Z. Physiol. Chem., 61, 272 (1941).

21. R.B. Turner, J. Am. Chem. Soc., 72, 579 (1950).

22. G.R. Pettit and T.R. Kasturi, J. Org. Chem., 26, 4557 (1961).

23. E. Caspi and S.N. Balasubramanyam, J. Org. Chem., 28, 3393 (1963).

24. J.T. Pinhey and K. Schaffner, Tetrahedron letters, 601 (1965).

25. J.T. Pinhey and K. Schaffner, Aust. J. Chem., 21, 1873 (1968).

26. M. Gorodetasky, N. Danieli and Y. Mazur, J. Org. Chem., 32, 760 (1967).

27. M.S. Ahmad and A.H. Siddiqi, Ind. J. Chem., 16B, 963 (1978).

28. Shafiullah and Ejaz A. Khan, Acta. Chim. Acad. Sci.(Hungry) (In press).

29. Ph.D. Thesis, N.K. Pillai, A.M.U. Aligarh (1973).

30. V.A. Petrow, J. Chem. Soc., 999 (1939).

31. J. Collines, Bull. Soc. Roy. Liege, 25, 428 (1956).

32. L.F. Fieser and M. Fieser, Steroid (Reinhold, New York)(1959).

33. S. Akagi, K. Tsuda, Chem. Pharm. Bull. (Tokyo), 9,464 (1961).

34. L.F. Fieser and S. Rajagopalan, J. Am. Chem. Soc., 71, 3939 (1949).

35. H. Aebli, C.A. Grob, and E. Schumacher, Helv. Chim. Acta., 41, 774 (1958).

36. C.W. Shoppee, R.E. Lack and S.K. Roy, J. Chem. Soc., 3767 (1962).

37. C.W. Shoppee, R.J. Bridgwater, D.N. Jones and G.H.R. Summers, J. Chem. Soc., 2492 (1956).

38. A. Fischer, W.J. Hardman, M.P. Hartshorn, Tetrahedron, 23, 159 (1967).

39. L.F. Fieser, J. Am. Chem. Soc., 75, 5421 (1953).

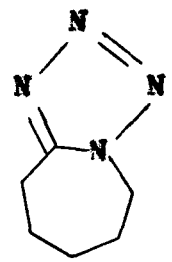
40. F. Sondheimer and Y. Mazur, J. Am. Chem. Soc., 79,2906 (1957).

41. G. Just and Keith St. C. Richardson, Cand. J. Chem., 42, 464 (1964).

THEORETICAL

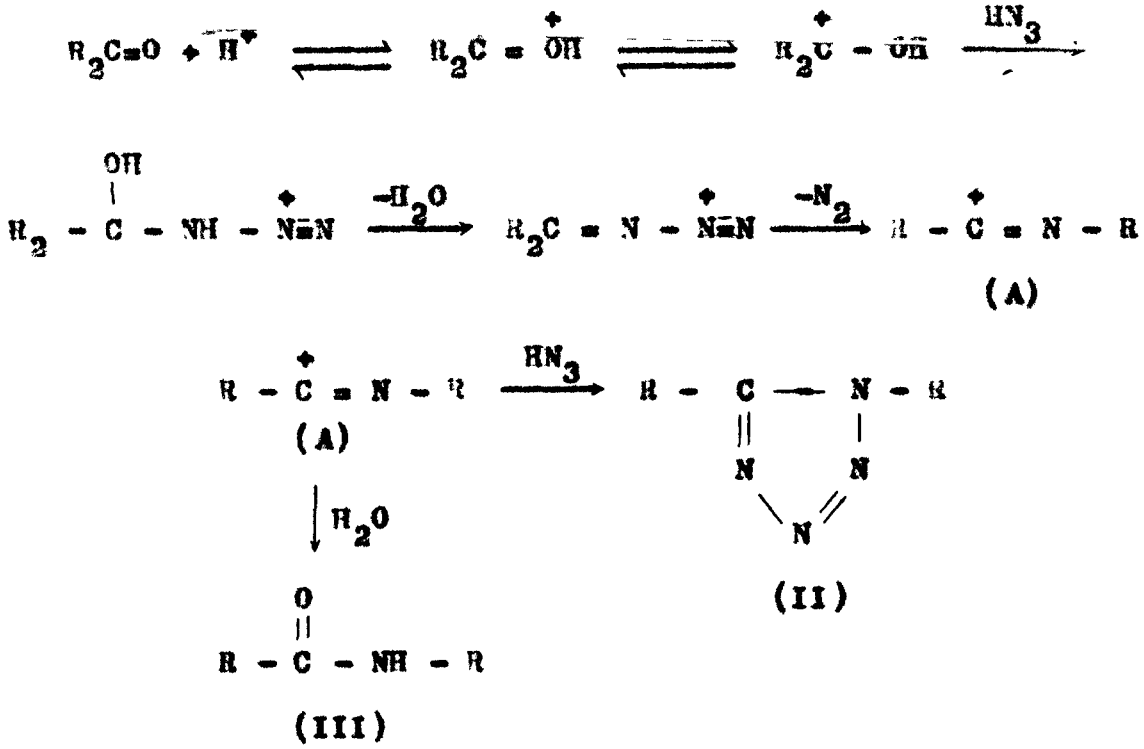
The heterocyclic compounds containing four nitrogen atoms and one carbon atom arranged in a fashion to constitute five membered ring with two alternate double bonds have been named as tetrazole. The first tetrazole was reported in 1885 by Bladin[1,2].

An excellent review, touching upon almost every aspect of tetrazole chemistry is given by Benson[3]. Tetrazoles have found important biological as well as non-biological applications. These have been applied in explosives as compounds of initiating compositions and in propellants, and a few of their salts are used in primers. They have also been used as binders in composite propellants, match compositions and as catalyst in polymerization. They are of use in fibre, dyestuff and textile industries and have applications in photography also. On the biological side the best known is pentamethylene tetrazole (Metrazole)(1) which is a potent stimulant of the central nervous system and is used clinically to counteract intoxication due to overdosage of barbiturates[4]. It has also been used to produce convulsions in the shock treatment of certain psychoses. Stimulant, depressant, sedative, analgestic, anticonvulsant, hypotensive and andrenergic blocking action are exhibited by a number of tetrazoles.



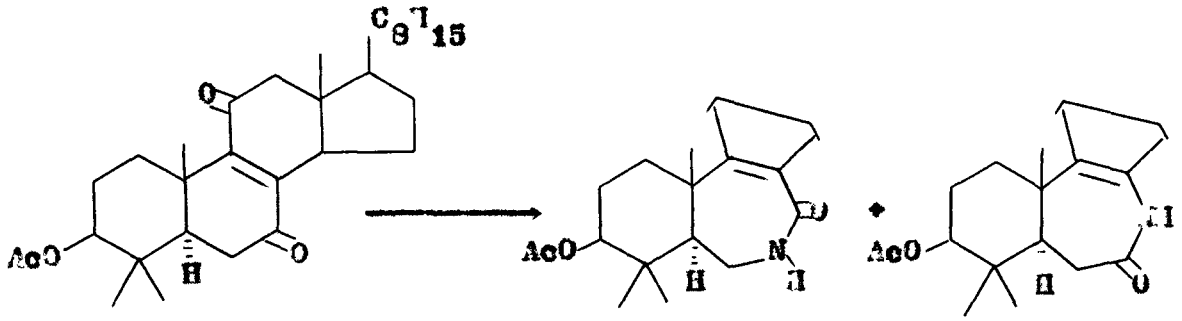
(I)

With the realization of the above mentioned applications of the tetrazoles, organic chemists directed their attention towards their synthesis. The most valuable method discovered by Schmidt[5] for the synthesis of tetrazoles is the rearrangement reaction between ketones and hydrazoic acid in the presence of strong acids. Smith[6] has given a probable mechanism for this transformation. Upon reacting with one mole of the hydrazoic acid, the ketone is converted to the intermediate imidocarbonium ion (A) which then reacts with the second mole of hydrazoic acid to form the tetrazole (II). Combination of hydrazoic acid with the imidocarbonium ion to form a tetrazole (II) competes with reaction of the imidocarbonium ion with water to form an N-substituted amide (III).

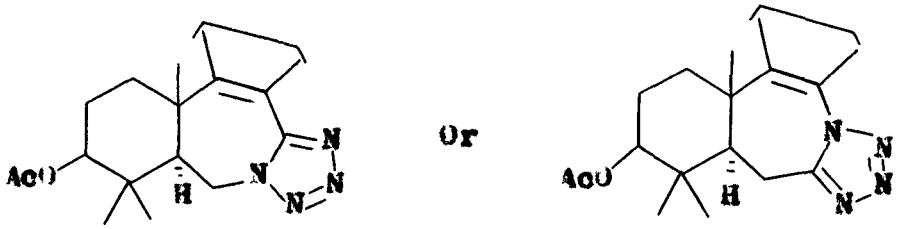


Steroidal Tetrazoles

Probably the first example of the formation of a tetrazole in steroid and triterpenoid field was given by Barnes et al.[7] in 1953. They treated 7, 11-dioxolanost-8-en-3β-yl acetate (IV) with hydrazoic acid and obtained in addition to two isomeric monolactams (V) and (VI), a tetrazole (VII or VIII).



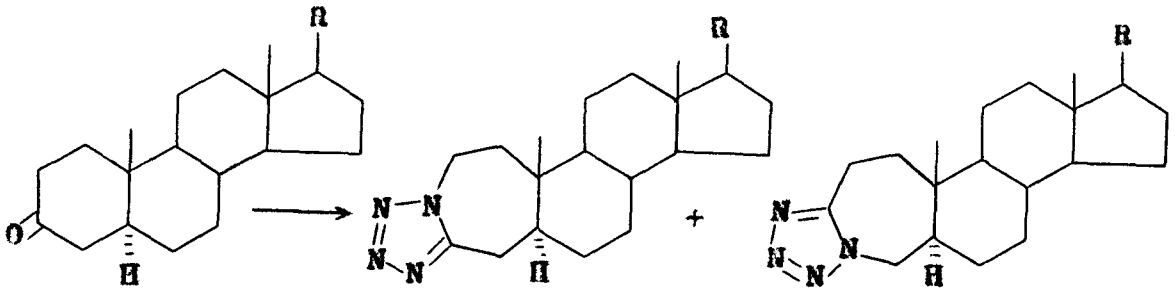
(IV) (V) (VI)



(VII) (VIII)

Meehoulam[8] reported the synthesis of a number of ring-A fused steroidal tetrazoles and claimed some of them to possess antifertility and antispermatogenic activities. He subjected

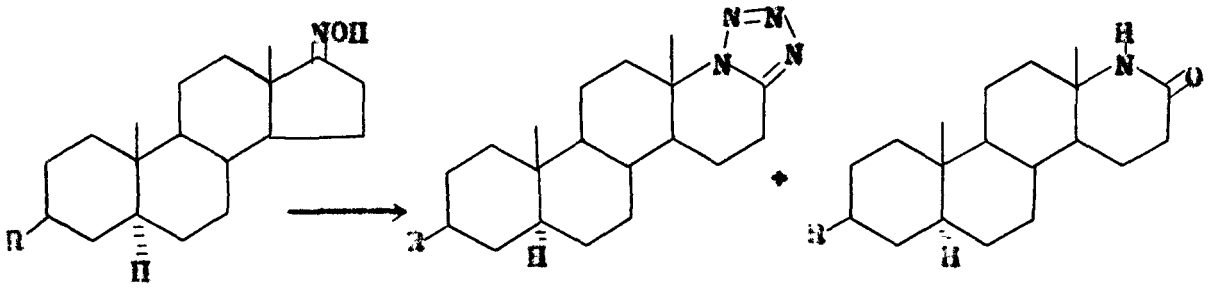
5α-cholestan-3-one (IX) and 17β-hydroxy-5α-androstan-3-one (XII) to Schmidt reaction using excess of hydrazoic acid which gave a mixture of isomeric tetrazoles (X, XI) and (XIII, XIV), respectively, containing 3-aza-A-homo-[3,4-d]tetrazole and 4-aza-A-homo-[4,3-d]tetrazole system.



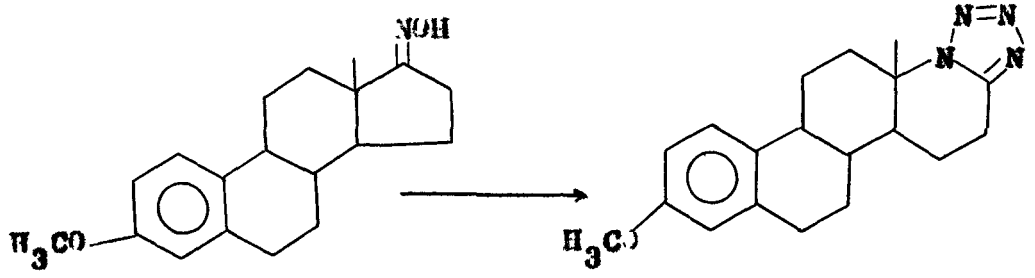
R	R	R
(IX) C_8H_{17}	(X) C_8H_{17}	(XI) C_8H_{17}
(XII) OH	(XIII) OH	(XIV) OH

Once the pharmacological potential of steroidal tetrazoles was realized, spate of attempts were made towards their synthesis and subsequently several papers appeared concerning their synthesis and biological activity. Cervantes et al.[9] of syntex group reported the formation of ring-D fused tetrazoles from the reaction of 17-ketoximes with an excess of sodium azide in the presence of sulphuric acid. 17-Hydroximino-5α-androstane(XV) afforded 17a-aza-D-homo-5α-androstano[17a,17-d]tetrazole (XVI) and the D-homolactam (XVII). Similarly the oxime (XVIII) yielded 3β-acetoxy-17a-aza-D-homo-5α-androstano[17a,17-d]tetrazole (XIX) and the lactam (XX). The oxime (XXI) gave 17a-aza-3-hydroxy-

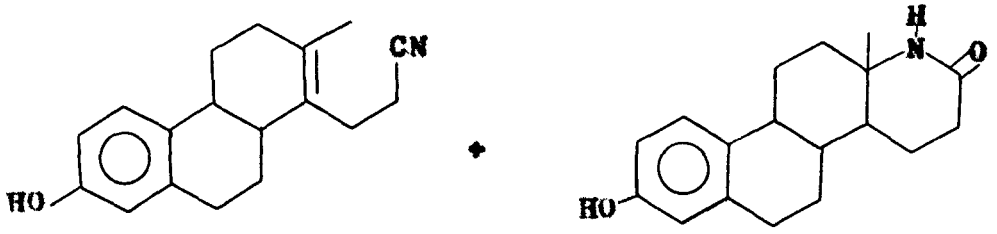
D-homoestra-1,3,5(10)-trieno[17a,17-d]tetrazol-3-methyl ether (XXII) along with the seco nitrile (XXIII) and lactam (XXIV) under similar reaction conditions.



R		R		R	
(XV)	H	(XVI)	H	(XVII)	H
(XVIII)	OAc	(XIX)	OAc	(XX)	OAc

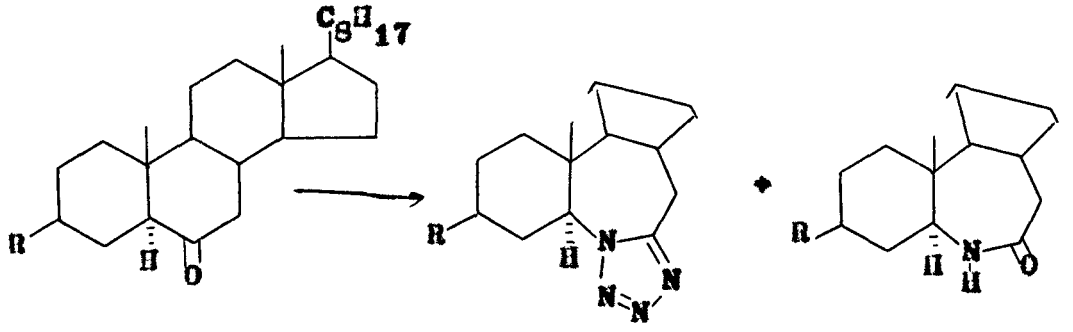


(XXI) (XXII)

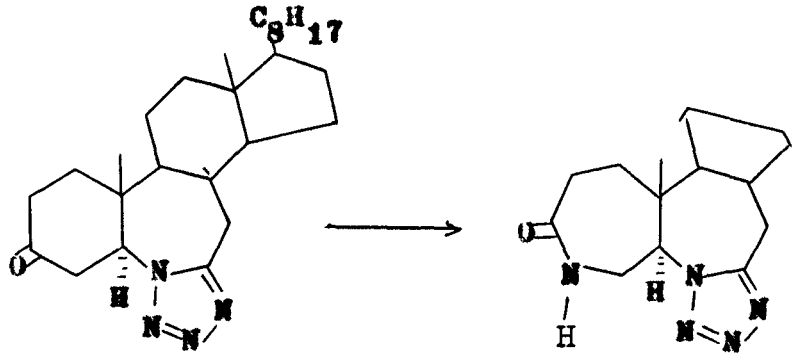


(XXIII) (XXIV)

A number of tetrazoles have been synthesized by Ahmad et al.[10] by treating 6-oxosteroids with excess of hydrazoic acid. 5α-Cholestan-6-one (XXV), its 3β-acetoxy (XXVI), 3β-hydroxy (XXVII) and 3β-chloro (XXVIII) analogues furnished the corresponding 6-aza-B-homo-5α-cholestano[6,7-d]tetrazoles (XXIX - XXXII) and lactams (XXXIII - XXXV). Jone s' oxidation of (XXXI) gave 6-aza-B-homo-3-oxo-5α-cholestano[6,7-d]tetrazole (XXXVI) which on treatment with an equimolar quantity of sodium azide afforded 4,6-diaza-A,B-bishomo-3-oxo-5α-cholestano[6,7-d] tetrazole (XXXVII).

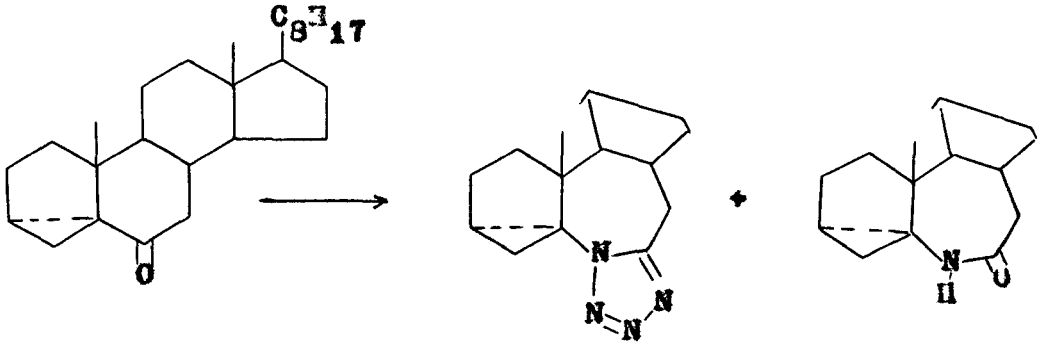


	R		R		R
(XXV)	H	(XXIX)	H	(XXXIII)	H
(XXVI)	OAc	(XXX)	OAc	(XXXIV)	OH
(XXVII)	OH	(XXXI)	OH	(XXXV)	Cl
(XXVIII)	Cl	(XXXII)	Cl		

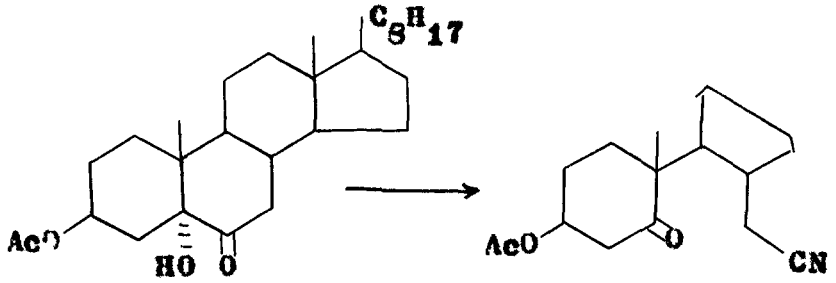


(XXXVI) (XXXVII)

Ahmad et al.[11] treated 3α,5-cyclo-5α-cholestan-6-one (XXXVIII) with excess of hydrazoic acid in the presence of BF_3-etherate and obtained 6-aza-B-homo-3α,5-cyclo-5α-cholestano [6,7-d]tetrazole (XXXIX) and the lactam (XL). Under similar reaction conditions, 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (XLI) afforded 3β-acetoxy-5-oxo-5,6-secocholestan-6-nitrile (XLII).



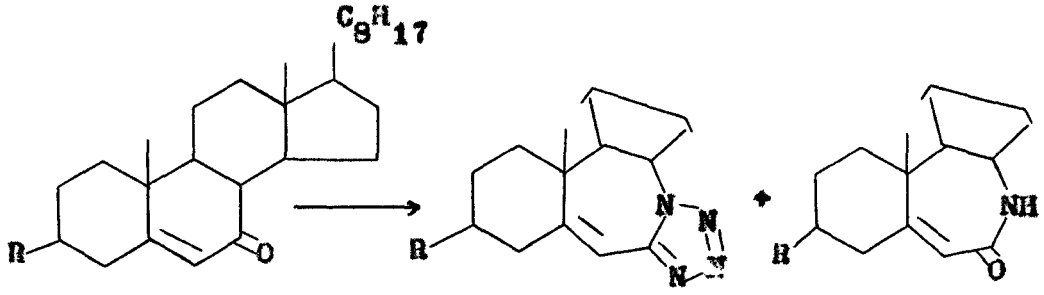
(XXXVIII) (XXXIX) (XL)



(XLI) (XLII)

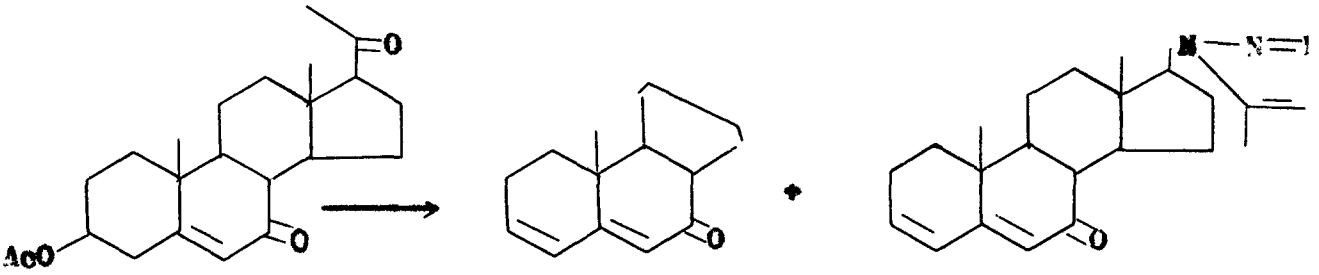
3 -Chlorocholest-5-en-7-one (XLIII), on treatment with excess of hydrazoic acid yielded 3 -chloro-7a-aza-B-homocholest-5-eno[7a,7-d]tetrazole (XLIV) and the lactam (XLV). Cholest-5-en-7-one (XLVI) under similar reaction conditions gave

7a-aza-B-homocholest-5-eno[7a,7-d]tetrazole (XLVII) and the lactam (XLVIII).

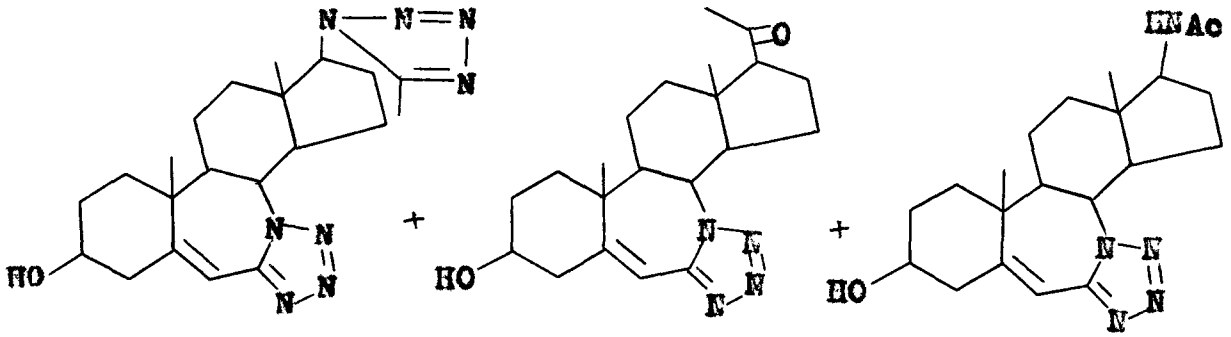


	R		R		R
(XLIII)	Cl	(XLIV)	Cl	(XLV)	Cl
(XLVI)	H	(XLVII)	H	(XLVIII)	H

Singh et al.[12] treated 3β-acetoxypregn-5-ene-7,20-dione (XLIX) with excess of hydrazoic acid-BF_3 etherate in chloroform which yielded 17β-(5-methyl tetrazol-1-yl)-7a-aza-B-homoandrost-5-eno[7a,7-d]tetrazol-3β-ol (LII), 17β-acetamido-7a-aza-B-homoandrost-5-eno[7a,7-d]tetrazol-3β-ol (LIV), 3 -hydroxy-7a-aza-B-homopregn-5-eno[7a,7-d]tetrazol-20-one (LIII), pregn-3,5-diene-7,20-dione (L) and 17β-(5-methyl tetrazol-1-yl) androsta-3,5-dien-7-one (LI).

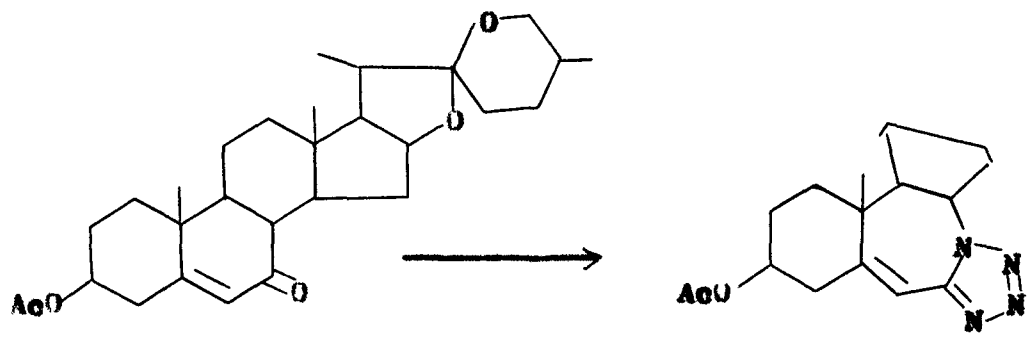


(XLIX) (L) (LI)



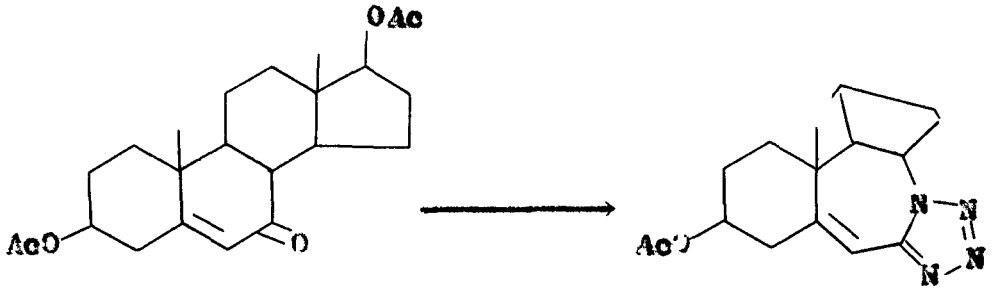
(LII) (LIII) (LIV)

(25 R)-7-oxo-5-spirostan-3β-yl acetate (LV)[13] on treatment with excess of hydrazoic acid -BF_3 etherate in chloroform afforded (25 R)-7a-aza-B-homo-5-spirostenoㄱ7a,7-dㄱtetrazol-3β-yl acetate (LVI).



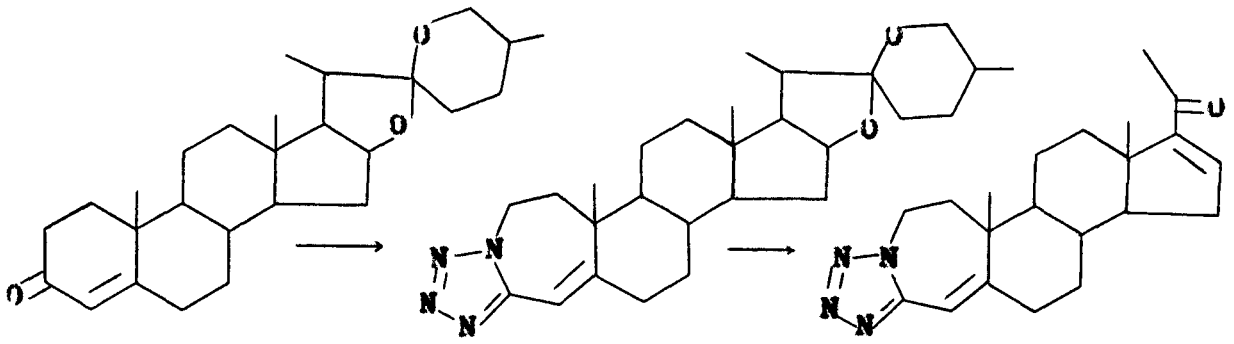
(LV) (LVI)

Similarly 7-oxo-5-androsten-3β,17β-diol diacetate (LVII) gave 7a-aza-B-homo-5-androsteno[7a,7-d]tetrazol-3β,17β-diol diacetate (LVIII).



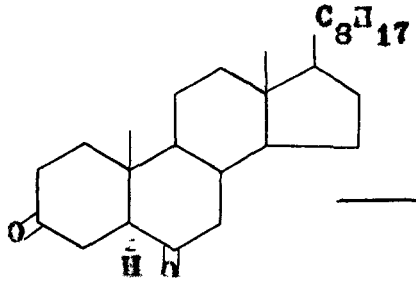
(LVII) (LVIII)

With the interest of obtaining tetrazolosteroids capable of affecting the nervous system, Singh et al.[14] treated (25 R)-spirost-4-en-3-one (LIX) with excess of hydrazoic acid to furnish a tetrazole which was shown to be 3-aza-A-homo-(25 R)-spirost-4a-eno[3,4-d]tetrazole (LX). The tetrazole (LX) on Marker degradation gave 3-aza-A-homopregna-4a,16-dieno[3,4-d]tetrazol-20-one (LXI).

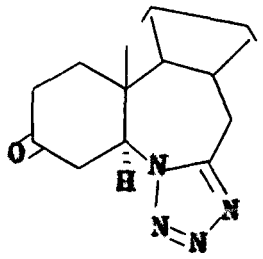


(LIX) (LX) (LXI)

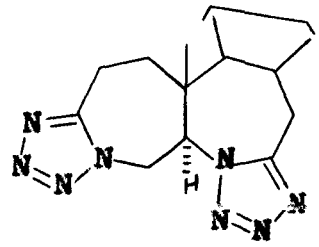
Ahmad et al.[15] treated 5α-cholestane-3,6-dione (LXII) with excess of hydrazoic acid and reported the formation of 6-aza-B-homo-3-oxo-5α-cholestano[6,7-d]tetrazole (LXIII), 4,6-diaza-A,B-bishomo-5α-cholestano[3,4-d][6,7-d]bistetrazole (LXIV) and 3,6-diaza-A,B-bishomo-5α-cholestano[3,4-d][6,7-d] bistetrazole (LXV). 5-Hydroxy-5α-cholestane-3,6-dione (LXVI) under similar treatment provided cholest-4-ene-3,6-dione (LXVII), 4-aza-A-homo-5-hydroxy-6-oxo-5α-cholestano[3,4-d]tetrazole (LXVIII) and 4-aza-A-homo-3,5a-dioxo-5,6-secocholestano-6-tetrazole (LXIX).



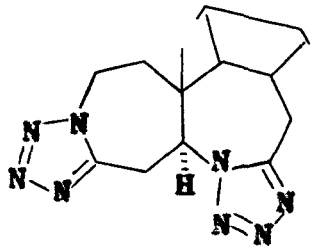
(LXII)



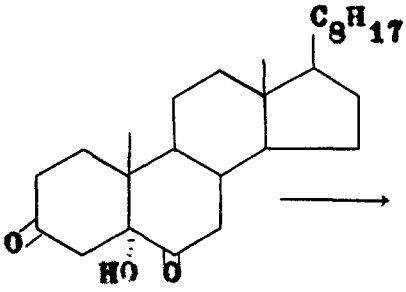
(LXIII)



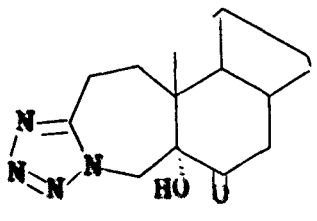
(LXIV)



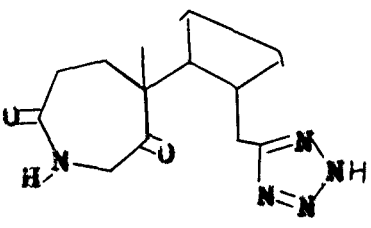
(LXV)



(LXVI)

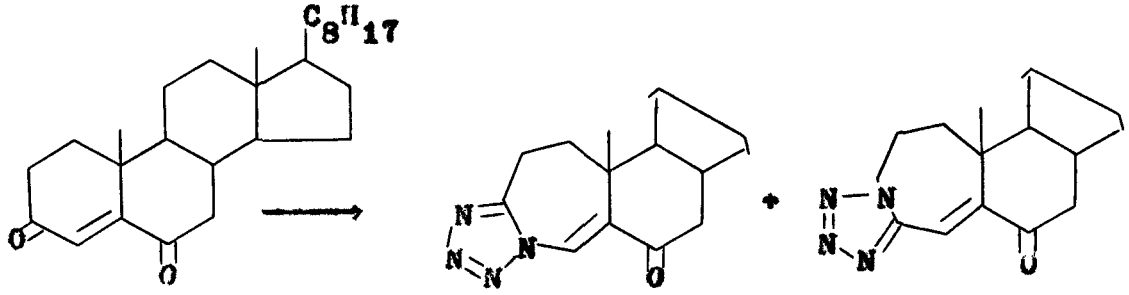


(LXVIII)

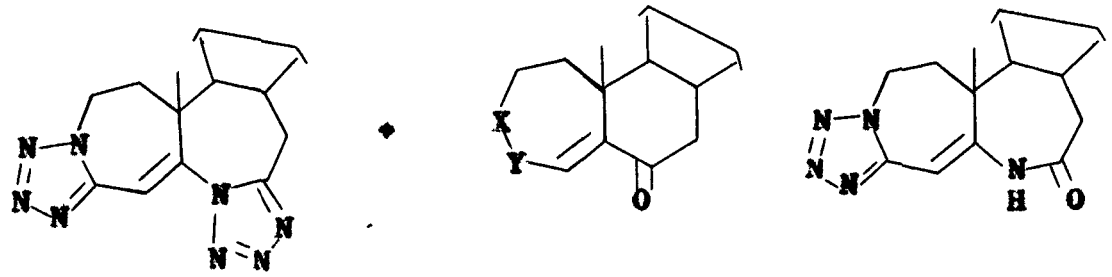


(LXIX)

Cholest-4-ene-3,6-dione (LXVII)[15] furnished 4-aza-A-homo-6-oxocholest-4a-eno[3,4-d]tetrazole (LXX), 3-aza-A-homo-6-oxocholest-4a-eno[3,4-d]tetrazole (LXVI), 3,6-diaza-A,B-bishomocholest-4a-eno[3,4-d][6,7-d]bistetrazole (LXXII), isomeric lactams (LXXIII), (LXXIV) and 3,6-diaza-A,B-bishomo-7-oxocholest-4a-eno[3,4-d]tetrazole (LXXV) under similar reaction conditions.



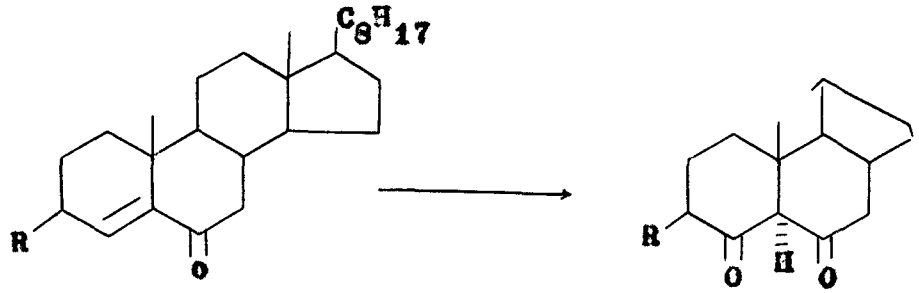
(LXVII) (LXX) (LXXI)



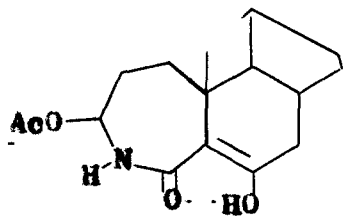
		X	Y
(LXXII)	(LXXIII)	NH	CO
	(LXXIV)	CO	NH

(LXXV)

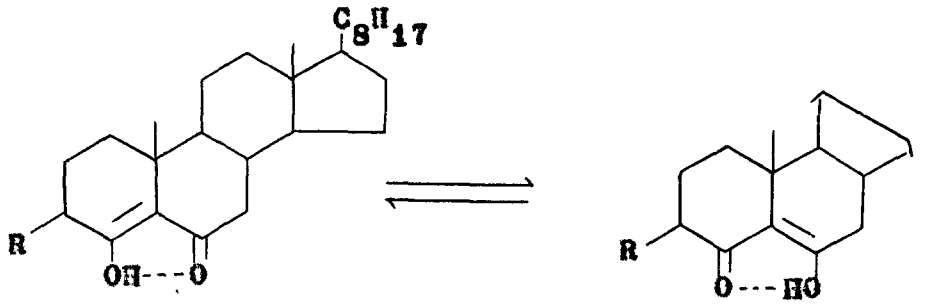
Reaction of cholest-4-en-6-one (LXXVI)[15] with excess of hydrazoic acid provided exclusively (LXXVII) in equilibrium with its tautomeric forms (LXXVIIa) and (LXXVIIb). Reaction of 3β-acetoxycholest-4-en-6-one (LXXVIII) provided 3β-acetoxy-5α-cholestane-4,6-dione (LXXIX) in equilibrium with the tautomeric forms (LXXIXa-LXXIXb), 3β-acetoxy-4-aza-A-homo-6-hydroxycholest-5-en-4a-one (LXXX). Under similar conditions, 6β-bromocholest-4-en-3-one (LXXXI) furnished 3-aza-A-homo-cholesta-4a,6-dieno [3,4-d]tetrazole (LXXXII).



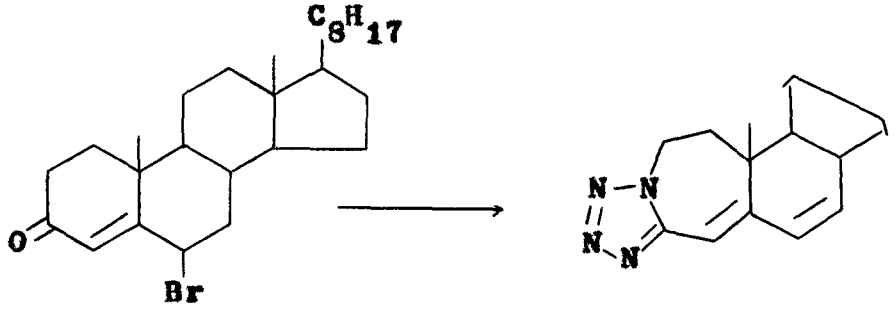
	R		R
(LXXVI)	H	(LXXVII)	H
(LXXVIII)	OAc	(LXXIX)	OAc



(LXXX)

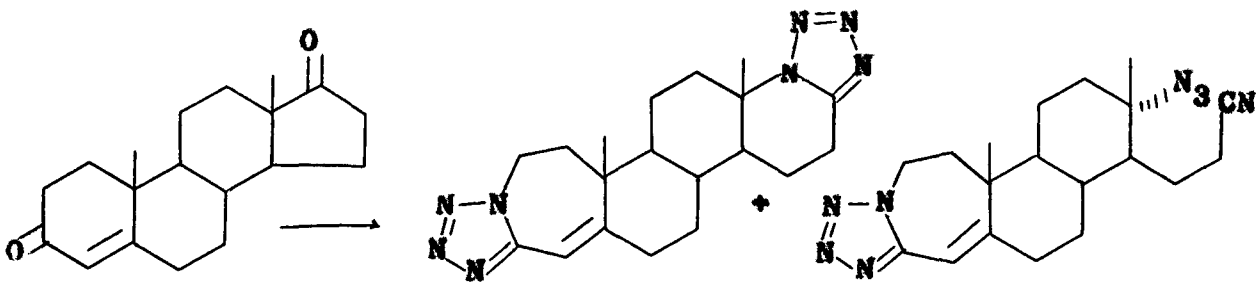


	R		R
(LXXVIIa)	H	(LXXVIIb)	H
(LXXIXa)	OAc	(LXXIXb)	OAc



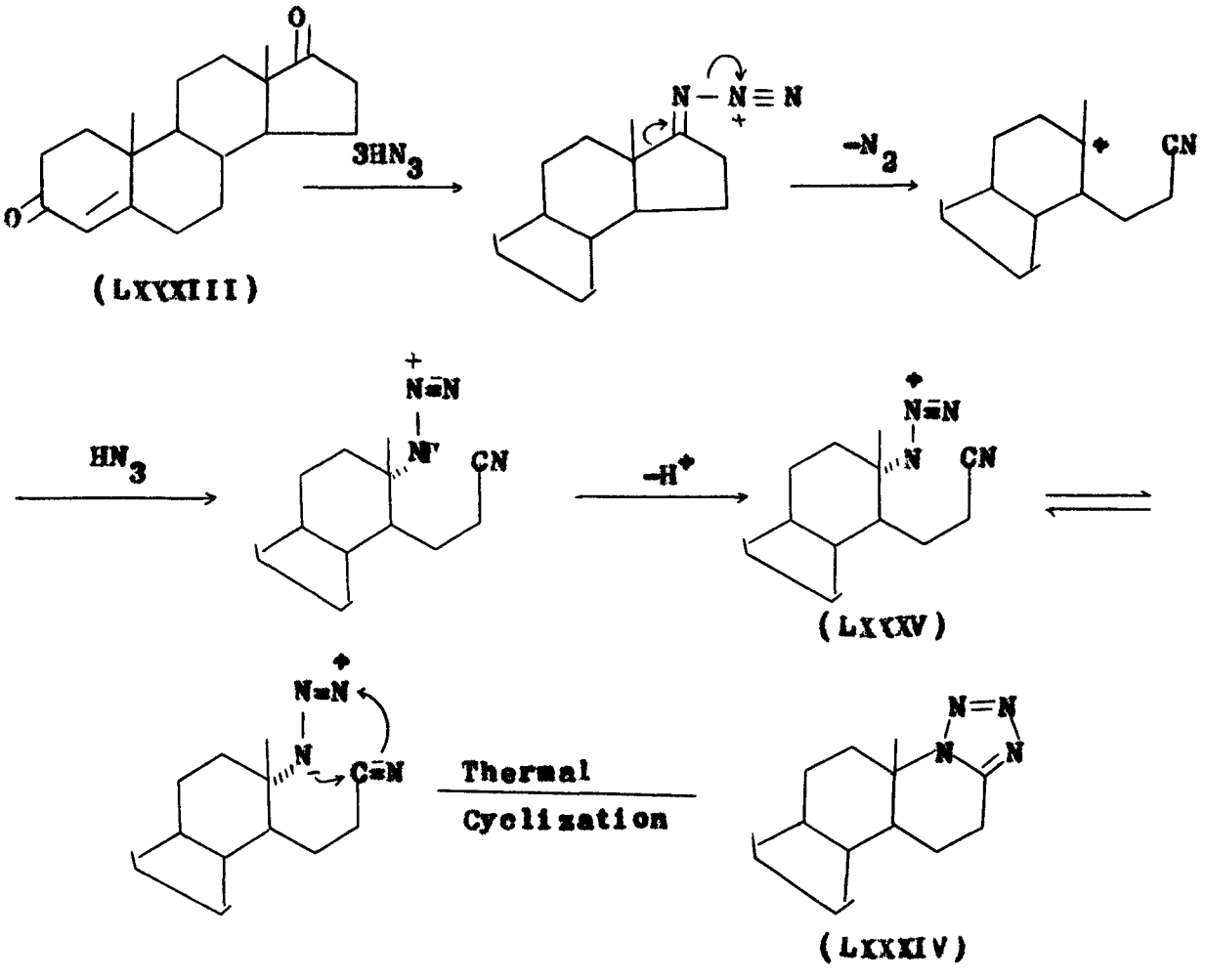
(LXXXI) (LXXXII)

Singh et al.[16,17] have reported that androst-4-ene-3,17-dione (LXXXIII) on treatment with excess of hydrazoic acid -BF_3 etherate in chloroform yielded the expected 3,17a-diaza-A,D-bishomoandrost-4a-eno[3,4-d][17a,17-d]bistetrazole (LXXXIV) and an unusual product, 13,17-seco-13α-azido-A-homoandrost-4a-eno[3,4-d]tetrazol-17-nitrile (LXXXV). The azido nitrile function in (LXXXV) cyclised on heating to give (LXXXIV). This is claimed to be the first instance of the isolation of an azidonitrile formed under Schmidt reaction conditions and its thermal cyclisation to a tetrazole.



(LXXXIII) (LXXXIV) (LXXXV)

To account for this novel cleavage of 17-oxosteroid (LXXXIII) to azido nitrile (LXXXV) and its subsequent cyclization to tetrazole (LXXXIV), the following mechanism was proposed.

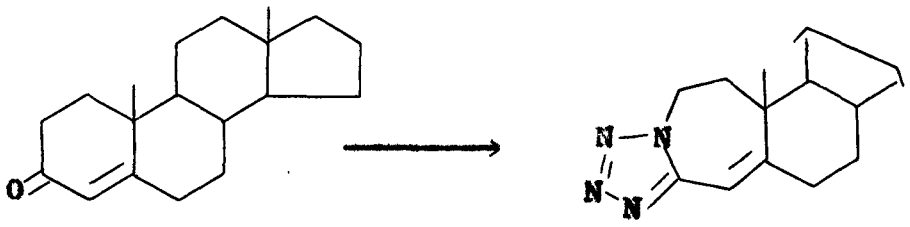


(LXXXIII)

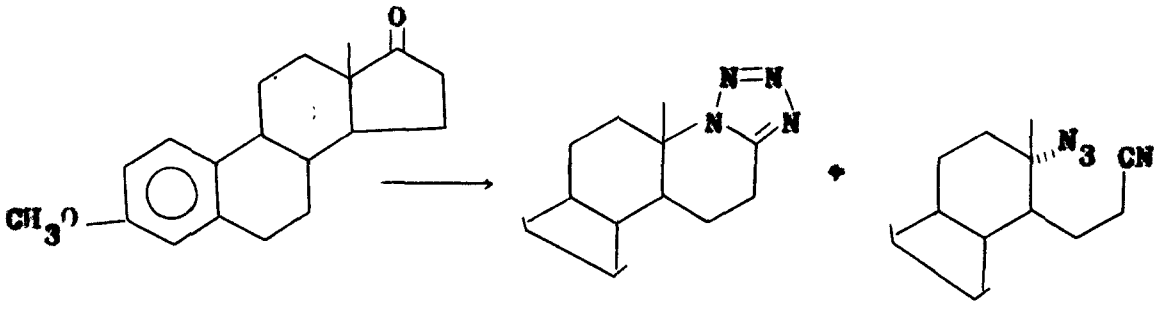
(LXXXV)

(LXXXIV)

4-Androsten-3-one (LXXXVI)[16] provided 3-aza-A-homo-4a-androsteno[3,4-d]tetrazole (LXXXVII), while estrone methyl ether (LXXXVIII) gave 3-methoxy-17a-aza-D-homo-1,3,5(10)-estratrieno[17a,17-d]tetrazole (LXXXIX) and 3-methoxy-13,17-seco-13α-azido-1,3,5(10)-estratrieno-17-nitrile (XC) under identical reaction conditions. The azido nitrile (XC) on thermal cyclization provided tetrazole (LXXXIX).

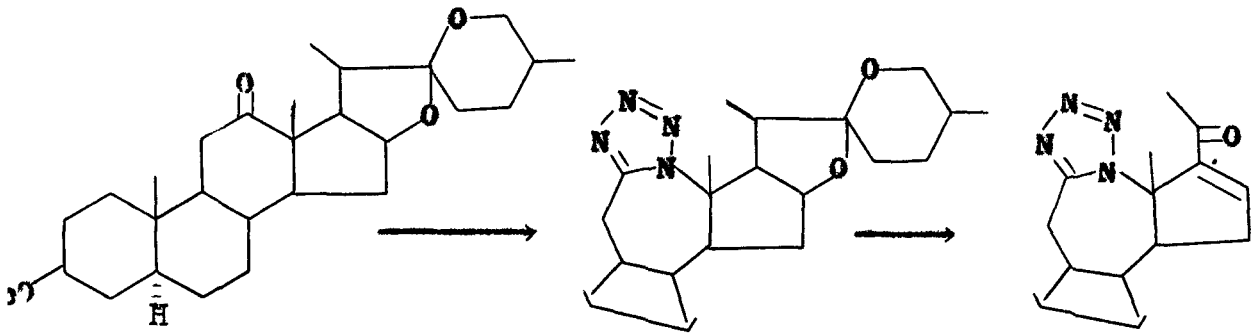


(LXXXVI) (LXXXVII)



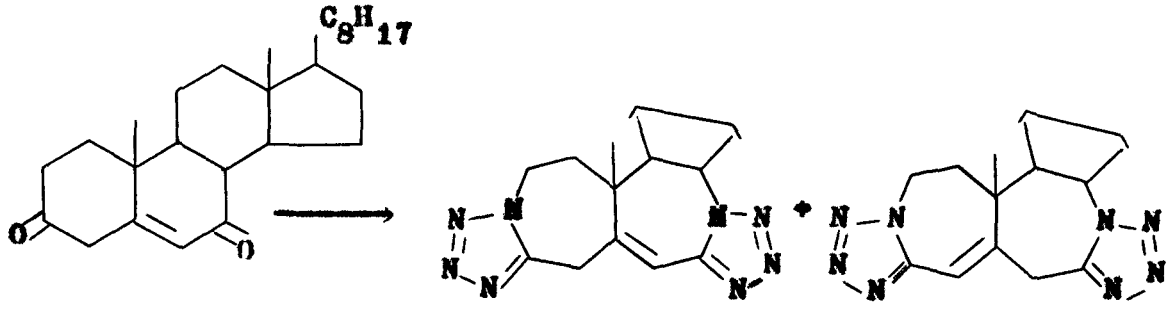
(LXXXVIII) (LXXXIX) (XC)

Singh et al.[19] treated hecogenin acetate (XCI) with excess of hydrazoic acid-BF_3 etherate and reported (25 R)-12a-aza-C-homo-5α-spirostano[12a,12-d]tetrazol-3β-yl acetate (XCII) as the sole product. The tetrazole (XCII) on Marker degradation gave 12a-aza-20-oxo-C-homo-5α-pregn-16-eno[12a,12-d]tetrazol-3β-yl acetate (XCIII).



(XCI) (XCII) (XCIII)

Cholest-5-ene-3,17-dione (XCIV)[20] on similar treatment gave 3,7a-diaza-A,B-bishomo-5-cholesteno[3,4-d][7a,7-d] bistetrazole (XCV) and its Δ^{4a}-isomer (XCVI).



(XCIV) (XCV) (XCVI)

Table - 1

Spectral data of some steroidal tetrazoles

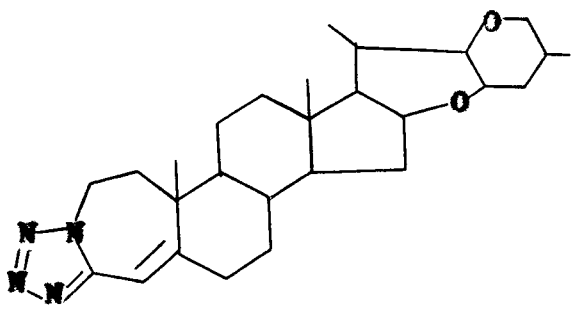
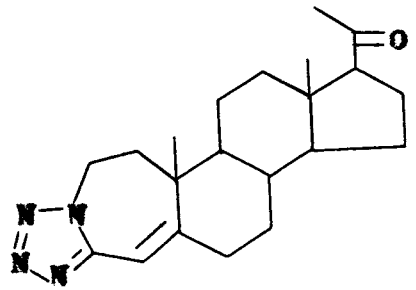
Compound	N.M.R. δ (ppm)	I.R. ν max (cm^{-1})	U.V. λ max (nm)(logϵ)	Ref.
 (LX)	6.49s (C4a-H), 4.50m (C2-H_2), 1.27 (C10-CH_3)	1650 (C=C), 1530, 1450, 1380(C=N, N=N)	243 (4.23)	14
 (LXI)	6.50s (C4a-H), 4.50m (C2-H_2), 1.23 (C10-CH_3)	1660 (C=C), 1520, 1445, 1375 (C=N, N=N)	241 (4.41)	,,

Table - 1 (Contd.)

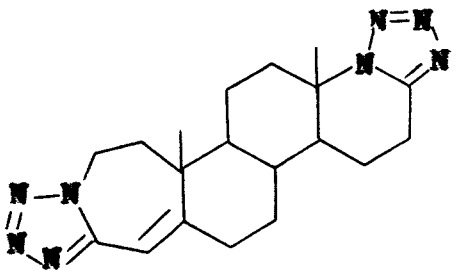
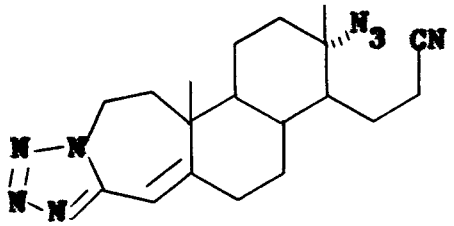
Compound	N.M.R. δ (ppm)	I.R. ν max (cm^{-1})	U.V. λ max (nm)(log ϵ)	Ref.
 (LXXXIV)	6.58s (C4a-H), 4.55m (C2-H_2), 3.0m(C16-H_2), 1.46s (3H), 1.34s (3H)(angular methyl protons)	1650(C=C), 1530, 1450 (C=N, N=N)	242 (4.25)	16,17
 (LXXXV)	6.57s (C4a-H), 4.56 (C2-H_2), 2.49m (NC-C16-H_2), 1.20 (3H), 1.16 (3H) (angular methyl protons)	3250 (CN), 2095 (N_3), 1650 (C=C), 1530, 1460 (C=N, N=N)	242 (4.23)	,,

Table - 1 (Contd.)

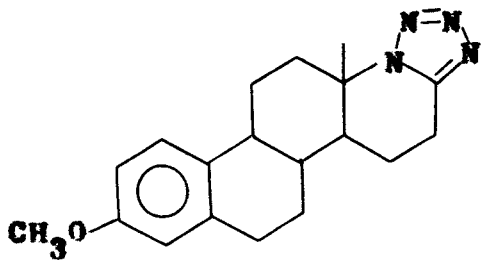
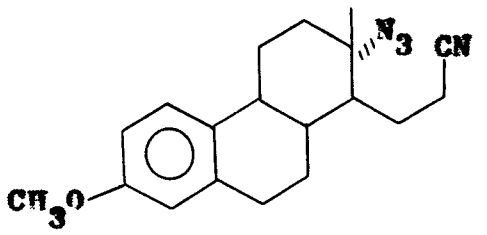
Compound	N.M.R. δ (ppm)	I.R. ν max (cm^{-1})	U.V. λ max (nm) (logϵ)	Ref.
 (LXXVIII)	7.1-7.3d(C1-H, J 8 Hz), 6.6-6.8d (C2-H, J 8 Hz), 6.6s (C4-H), 3.75 (OCH_3), 1.4s(C13-CH_3)	1580, 1500 (C=N, N=N)	278,287 (3.21, 3.17)	18
 (XC)	6.62-7.30(C1-H; C2-H; C4-H), 3.75s (OCH_3), 2.90m (NC-C16-H_2), 1.21 (C13-CH_3)	2252 (CN), 2101 (N_3), 1515, 1449 (C=N, N=N)	275 (3.25)	,,

Table - 1 (Contd.)

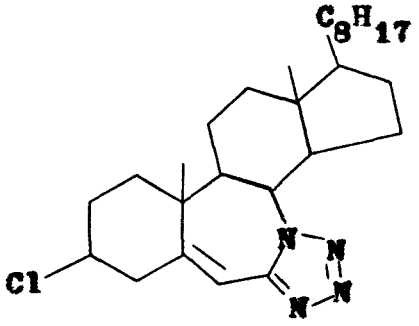
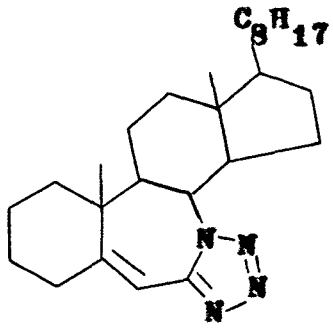
Compound	N.M.R. δ (ppm)	I.R. ν_{max} (cm^{-1})	U.V. λ_{max} (nm)(log ϵ)	Ref.
 (XLIV)	6.63s (C6-H), 4.21br (C3-βH), 3.81m (C3-αH), 1.33 (C10-CH_3), 0.80s (C13-CH_3)	1660 (C=C), 1505, 1470, 1380 (C=N, N=N), 765(C-Cl)	240 (4.13)	11
 (XLVII)	6.55s (C6-H), 4.22br (C8-βH), 1.23 (C10-CH_3), 0.81 (C13-CH_3)	1670 (C=C),1505, 1465, 1380 (C=N, N=N)	243 (4.10)	,,

Table - 1 (Contd.)

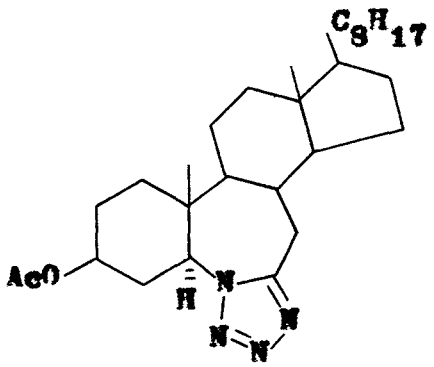
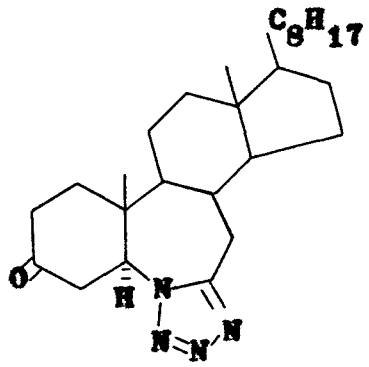
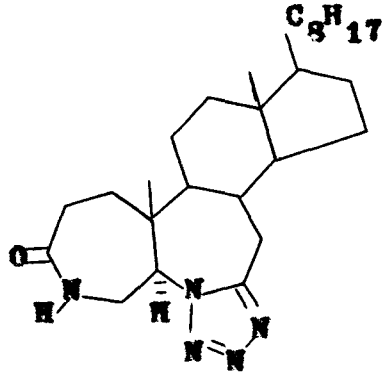
Compound	N.M.R. δ (ppm)	I.r. ν_{max} (cm^{-1})	U.V. λ_{max} (nm)	Ref.
 (XXX)	4.78br(C3-H), 4.45dd (C5-H; J 14 and 7 Hz), 3.4d (C7a-H; J 15 Hz), 2.06s (CH_3COO), 0.91 (C10-CH_3), 0.55 (C13-CH_3), 0.83 and 0.65 (remaining methyl protons)	1720(CH_3COO), 1525, 1455, 1360 (C=N, N=N)	-	16
 (XXVI)	4.66dd (C5-H; J 13 and 6 Hz), 3.5m ($C7a-H_2$), 0.91 (C10-CH_3), 0.68 (C13-CH_3), 0.81 and 0.73 (remaining methyl protons)	1722 (C=O), 1530, 1460, 1360(C=N, N=N)	-	10

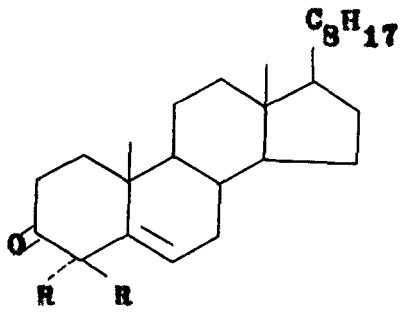
Table - 1 (Contd.)

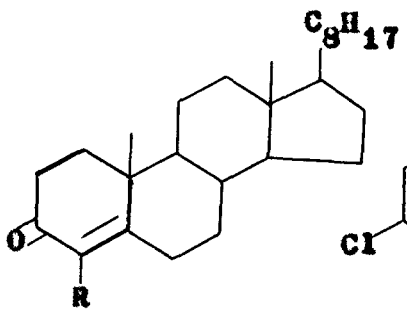
Compound	N.M.R. δ (ppm)	I.R. ν max (cm^{-1})	U.V. λ max. (nm)	Ref.
 (XXXVII)	7.0br (NH ; exchangeable with D_2O), 4.66br(C5-H), 4.06m (C4a-H_2), 3.41m (C7a-H_2), 0.91 (C10-CH_3), 0.45 (C13-CH_3), 0.81 and 0.65 (remaining methyl protons).	3340, 3200 (NH), 1690, 1640 (CONH) 1540, 1470, 1380 (C=N, N=N)	-	10

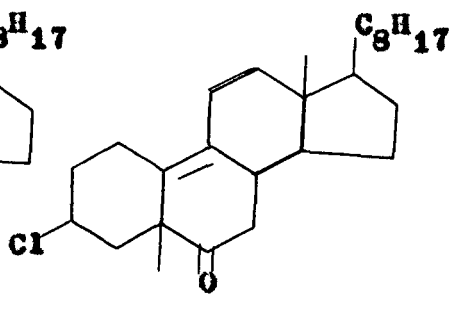
DISCUSSION

Steroidal tetrazoles have become of interest in recent years because of the discovery of biological activity associated with a number of tetrazoles and also because of their uses as potential drugs. As a result of this realization, synthesis of steroidal tetrazoles became a matter of much interest and consequently a number of papers appeared describing the preparation of tetrazoles from various steroidal ketones.

The present work describes the preparation of tetrazoles derived from hitherto unexplored steroidal ketones such as 4,4-dimethylcholest-5-en-3-one (XCVII), 4-methylcholest-4-en-3-one (XCVIII), its ethyl derivatives (XCIX), (C), and 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (CI).







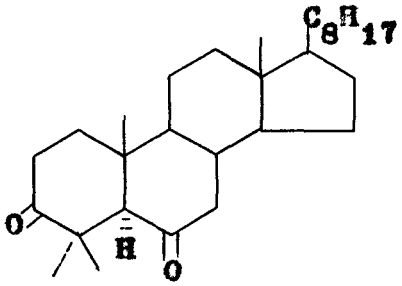
	R
(XCVII)	CH_3
(XCIX)	CH_2-CH_3

	R
(XCVIII)	CH_3
(C)	CH_2-CH_3

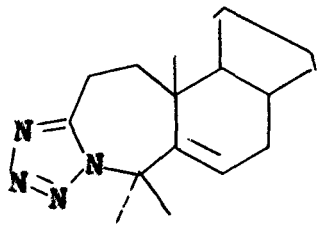
(CI)

Reaction of 4,4-dimethylcholest-5-en-3-one (XCVII) with an excess of hydrazoic acid

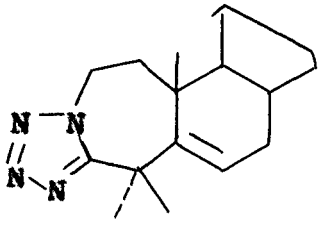
4,4-Dimethylcholest-5-en-3-one (XCVII) was treated with excess of hydrazoic acid solution (prepared according to the method described by Moural and Syhora[21]) in the presence of BF_3-etherate as catalyst. Usual work up of the reaction mixture and column chromatography over silica gel provided two compounds, m.p. 168° and 132°.



(CII)



(CIII)

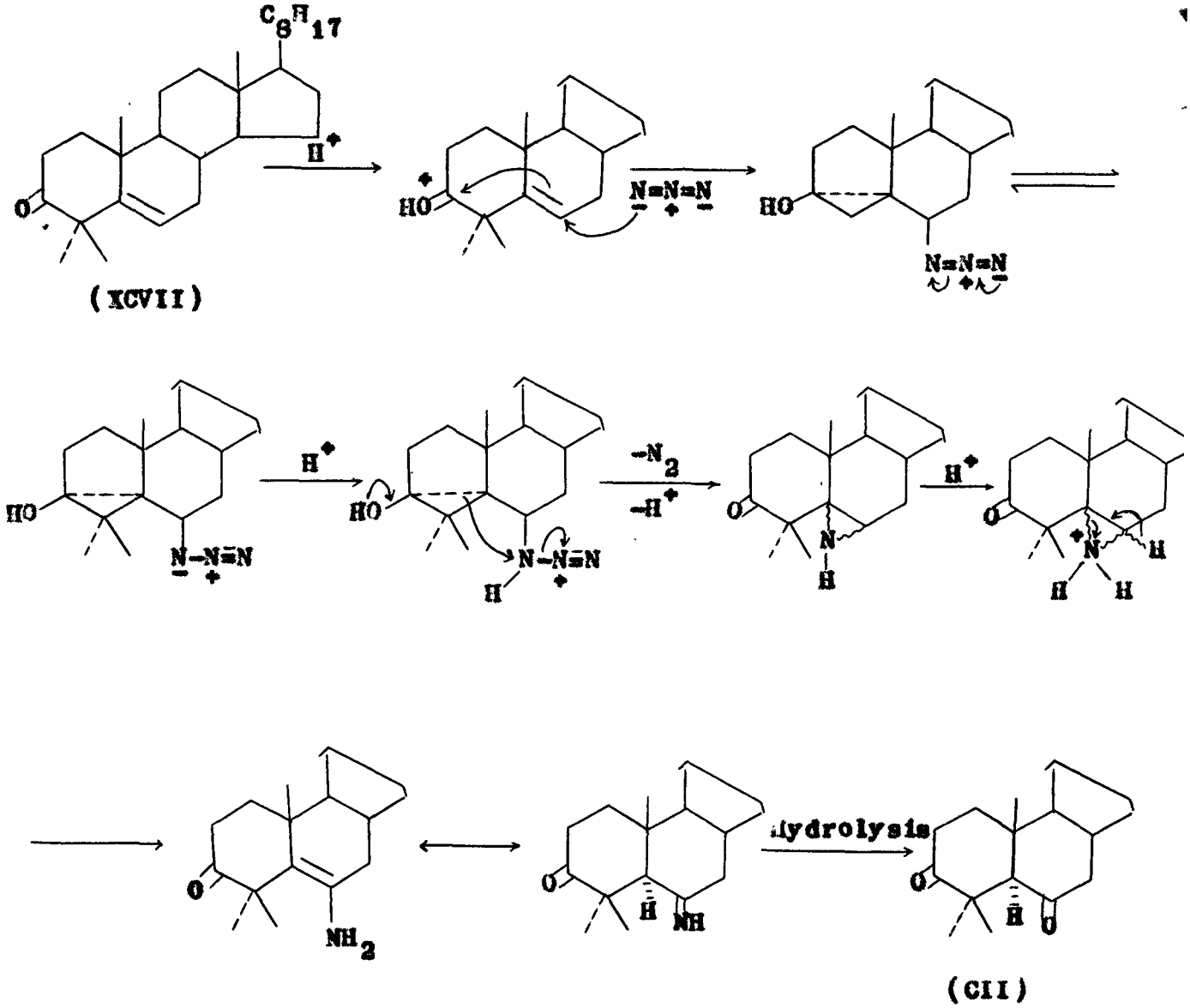


(CIV)

Characterisation of the compound, m.p. 168° as 4,4-dimethyl-5α-cholestane-3,6-dione (CII)

The compound, m.p. 168° was analysed correctly for $C_{29}H_{48}O_2$ which showed addition of one oxygen atom to the substrate. The I.R. spectrum of the compound displayed a strong band at 1700 cm^{-1} (C=O). No band for double bond was observed (Negative Tetranitromethane Test). The N.M.R. spectrum of the compound (CII) was clean in the downfield region and did not show signal for

vinylic proton. The spectrum showed signals only for methyl and methylene protons. The signal at δ 2.3 accounted for 4 methylene protons (C2-$\underline{H}_2$, C7-$\underline{H}_2$). Signals for C10-C$\underline{H}_3$ and C13-C$\underline{H}_3$ were appeared at δ 1.12 and 0.76 respectively. Other methyl protons were appeared at δ 0.95 and 0.85. The compound (CII) was found identical in all respects with the authentic sample[22]. To account for the formation of diketone (CII), from (XCVII) under Schmidt reaction conditions the following mechanism is being proposed.

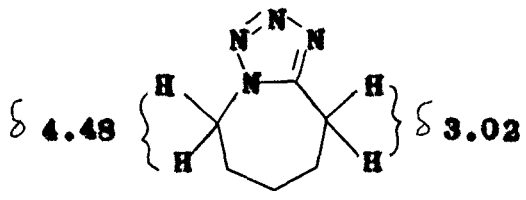


(CII)

Characterization of the compound, m.p. 132° as 4-aza-A-homo-4a,4a-dimethylcholest-5-eno[4,3-d]tetrazole (CIII)

The compound, m.p. 132° was analysed for $C_{29}H_{48}N_4$. The I.R. spectrum exhibited peaks at 1640 (C=C), 1510, 1460, 1375 cm^{-1} (C=N, N=N)[21,14], indicating the presence of tetrazole moiety in the compound. On the basis of elemental analysis and I.R. data, two isomeric structures can be written for the compound, m.p. 132°, i.e. 4-aza-A-homo-4a,4a-dimethylcholest-5-eno[4,3-d]tetrazole (CIII) or 3-aza-A-homo-4a,4a-dimethylcholest-5-eno[3,4-d] tetrazole (CIV). A clear distinction between two was made possible with the help of N.M.R. spectrum of the compound.

It has been reported by Di Maio and Permutti[23] that N.M.R. spectrum of the tetrazole of the type (CV) exhibits a two protons multiplet at δ 4.48 which is ascribable to the methylene group directly attached to the ring nitrogen atom and another two protons multiplet at δ 3.02 due to the methylene group adjacent to C=N fragment of the tetrazole moiety.

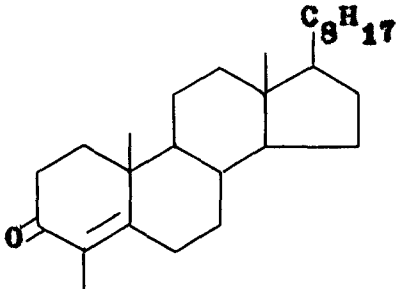


(CV)

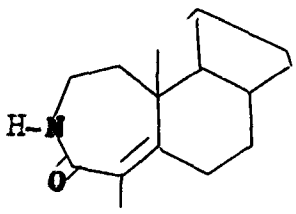
The N.M.R. spectrum of the compound, m.p. 132° exhibited a broad signal at δ 6.17 ascribable for a vinylic proton C6-H. A multiplet centred at δ 3.16 integrating for two protons is assigned to C2-H_2. The spectrum was almost clean in the region 4-5 which eliminated the 3-aza structure (CIV) and supported 4-aza structure (CIII) for the compound, m.p. 132°. The C4a-methyl protons appeared at δ 1.94 and 1.82. Other methyl signals were observed at δ 1.16 (C10-CH_3), 0.67 (C13-CH_3), 0.9 and 0.8 (remaining methyl protons). It is pertinent to mention that the insertion of nitrogen between C3 and C4 affects considerable downfield shift of the C4a-methyl protons.

Reaction of 4-methylcholest-4-en-3-one (XCVIII) with excess of hydrazoic acid

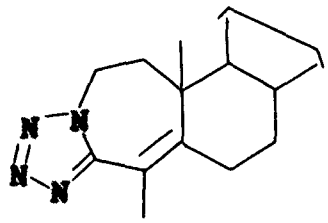
The reaction of ketone (XCVIII) with excess of hydrazoic acid in the manner described for (CII) afforded two compounds; a non crystallizable oil and a solid, m.p. 141°.



(XCVIII)



(CVI)



(CVII)

Characterization of the oil as 3-aza-A-homo-4a-methylcholest-4a-en-4-one (CVI)

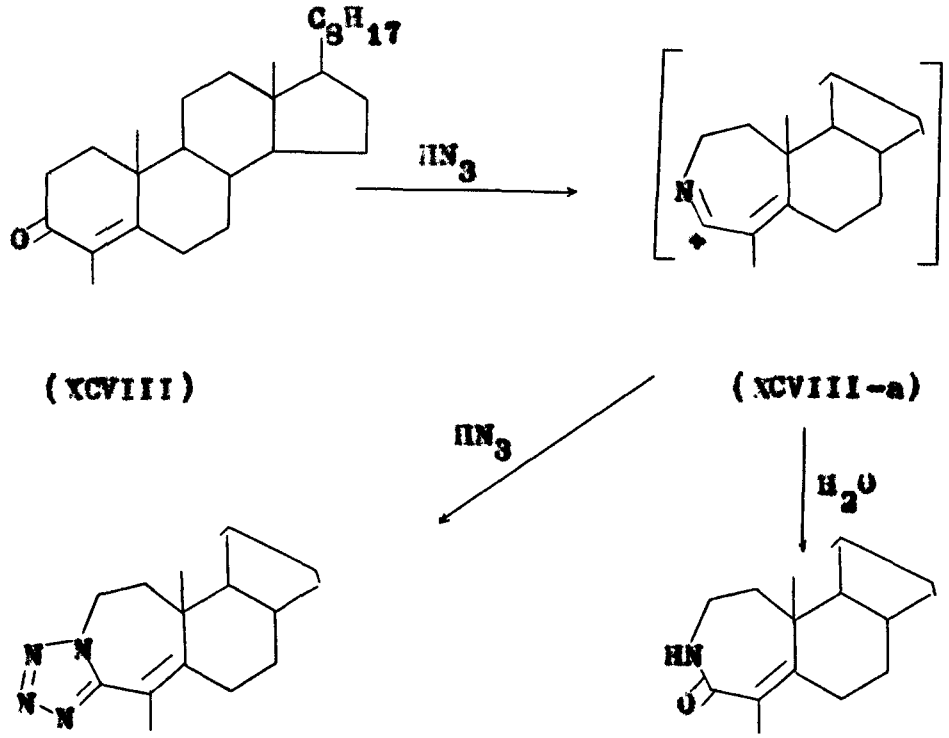
The oily compound was analysed for $C_{28}H_{47}NO$ which indicated the insertion of only one nitrogen atom in (XCVIII). I.R. spectrum exhibited bands at 3400 (-NH), 1650 (-NH-CO-) and 1635 cm^{-1}(C=C). On the basis of molecular composition and I.R. data, the compound under discussion was suspected to be a lactam. The N.M.R. spectrum of the compound gave broad signal at δ 3.6 integrating for two protons which can be ascribed to the C2-$\underline{H}_2$ in vicinity of nitrogen atom. The -N$\underline{H}$ signal was centred at δ 6.27 which was found exchangeable with deuterium. The signal for C4a-C$\underline{H}_3$ was observed at δ 2.2. Other methyl signals were seen at δ 1.21 (C10-C$\underline{H}_3$), 0.72 (C13-C$\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons). On the basis of these elemental and spectral data the compound is identified as 3-aza-A-homo-4a-methylcholest-4a-en-4-one (CVI). The lactam (CVI) was also obtained when the ketone (XCVIII) was treated with an unimolecular quantity of sodium azide in sulphuric acid.

Characterisation of the compound, m.p. 141° as 3-aza-A-homo-4a-methylcholest-4a-eno[3,4-d]tetrazole (CVII)

The compound , m.p. 141° was analysed for $C_{28}H_{46}N_4$. Its I.R. spectrum showed peaks at 1600 (C=C), 1510, 1450 and 1375 cm^{-1} (C=N, N=N). In N.M.R. spectrum, a broad multiplet appeared at 4.35 which was assigned to C2-$\underline{H}_2$. A sharp singlet at δ 2.31

integrating for three protons was ascribable to C4a-$\underline{CH}_3$. Other methyl signals were observed at δ 1.21 (C10-$\underline{CH}_3$), 0.65 (C13-$\underline{CH}_3$), 0.98 and 0.77 (remaining methyl protons). The downfield shift of signal for C4a-$\underline{CH}_3$ was justified since in addition to its being attached to vinylic carbon, it has tetrazole moiety in the vicinity. The U.V. spectrum of the compound (CVII) exhibited absorption maximum at 247 nm which further supported 3-aza structure.

The formation of 3-aza tetrazole (CVII) and 3-aza lactam (CVI) from (XCVIII) clearly indicates that both are derived from a common imidocarbonium ion intermediate (XCVIII-a). The formation of the tetrazole (CVII) and lactam (CVI) occurs via the following reaction pathways.

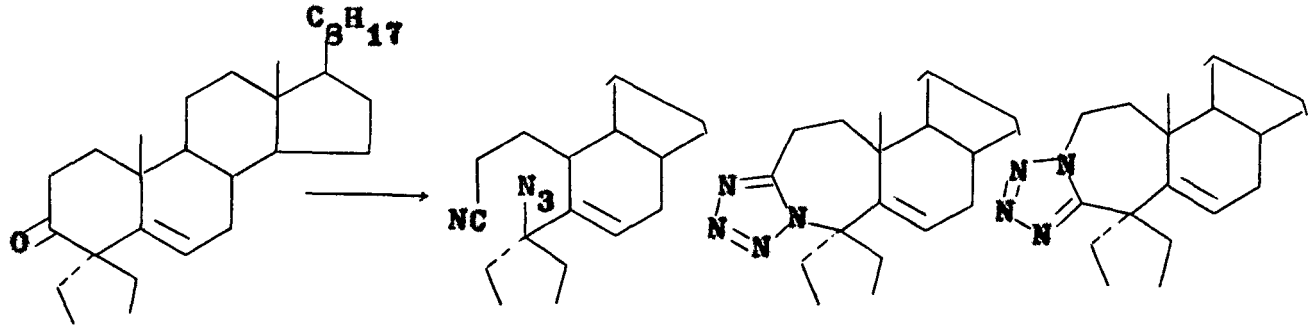


(XCVIII) (XCVIII-a)

(CVII) (CVI)

Reaction of 4,4-diethylcholest-5-en-3-one (XCIX) with excess of hydrazoic acid

The ketone (XCIX) was treated with excess of hydrazoic acid in usual manner. The usual work up of the reaction mixture and column chromatography over silica gel afforded two products; a non crystallizable oil and a solid, m.p. 135°.



(XCIX) (CVIII) (CIX) (CX)

Characterization of the oil, as 4,4-diethyl-3,4-seco-4β-azidocholest-5-en-3-nitrile (CVIII)

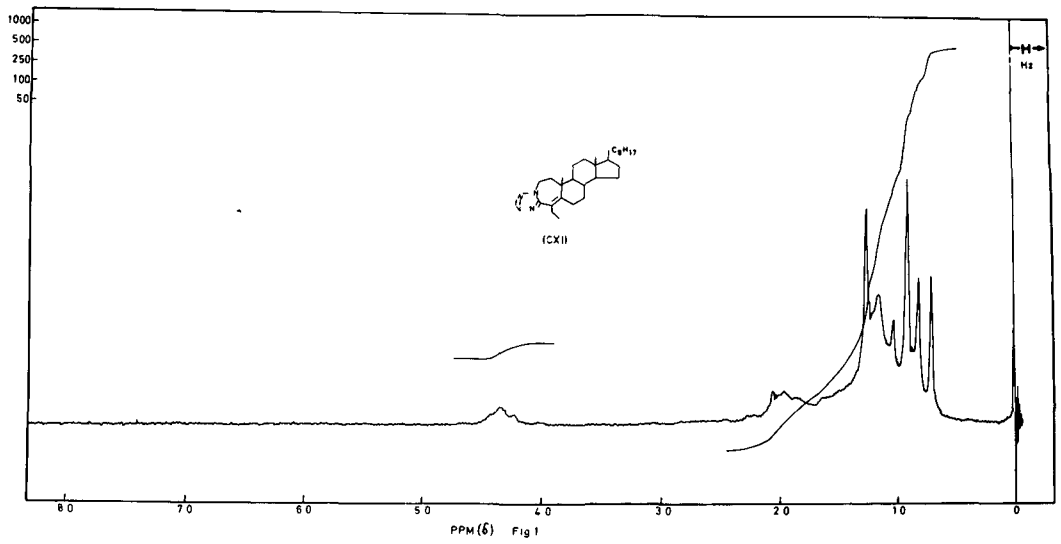
The oily compound was analysed for $C_{31}H_{52}N_4$. I.R. spectrum exhibited bands at 2240 (-C≡N), 2100 ($-N_3$)[18] and 1630 cm^{-1} (C=C). In its N.M.R. spectrum a broad multiplet centred at 5.28 integrating for one proton is ascribable to vinylic proton (C6-H). The absence of a signal in the region 3-4 indicated that azido group is present at C4. Methyl signals were observed at 1.08 (C10-CH_3), 0.68 (C13-CH_3), 0.91 and 0.81 (remaining methyl protons).

Characterization of the compound, m.p. 135° as 4-aza-A-homo-4a,4a-diethylcholest-5-eno[4,3-d]tetrazole (CIX)

The compound, m.p. 135° was analysed for $C_{31}H_{52}N_4$. I.R. spectrum showed peaks at 1635 (C=C), 1510, 1450 and 1380 cm^{-1} (C=N, N=N). On the basis of this data, two isomeric structures can be written for the compound, m.p. 135° i.e. 4-aza-A-homo [4,3-d]tetrazole (CIX) and 3-aza-A-homo[3,4-d]tetrazole (CX). A clear distinction between the two was made with the help of N.M.R. spectrum which exhibited a multiplet centred at δ 5.86 ascribable for a vinylic proton (C6-H). A multiplet at δ 2.96 integrating for two protons is assigned to H_2C2-CN which supports the structure (CIX). The methyl protons were appeared at δ 0.9 (C10-CH_3), 0.67 (C13-CH_3), 0.83 and 0.80 (remaining methyl protons).

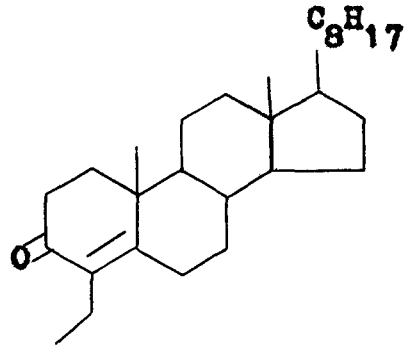
Reaction of 4-ethylcholest-4-en-3-one (C) with excess of hydrazoic acid

4-Ethylcholest-4-en-3-one (C) was treated with excess of hydrazoic acid in usual fashion. Reaction mixture after usual work up and column chromatography over silica gel yielded two compounds; m.p. 96° and 72°.

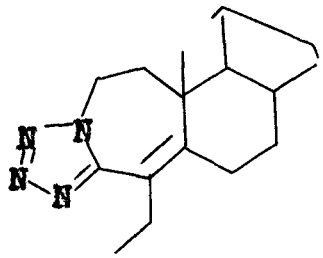


(CXI)

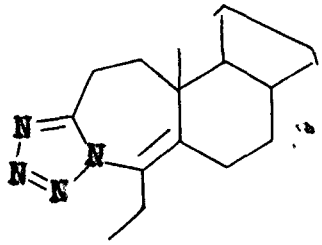
Fig 1



(C)



(CXI)

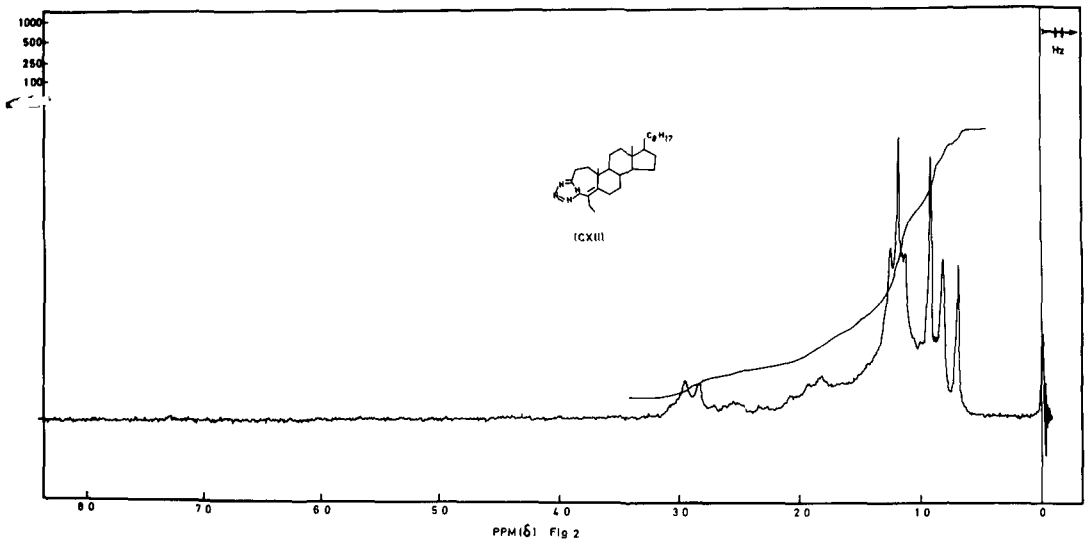


(CXII)

Characterization of the compound, m.p. 96° as 3-aza-A-homo-4a-ethylcholest-4a-eno[3,4-d]tetrazole (CXI)

The compound, m.p. 96° was analysed for $C_{29}H_{48}N_4$. The molecular composition of the compound indicated the presence of the tetrazole moiety. The I.R. spectrum showed bands at 1600 (C=C), 1510, 1450, 1390 cm^{-1} (C=N, N=N). The N.M.R. spectrum of (CXI) (Fig. 1) exhibited a characteristic multiplet centred at 4.39 for two protons which can be ascribed to $\underline{H}_2C2$-N-. On the basis of molecular composition and spectral data the compound, m.p. 96° has been identified as 3-aza-A-homo-4a-ethylcholest-4a-eno[3,4-d] tetrazole (CXI). The methyl protons were appeared at δ 1.18 (C10-$C\underline{H}_3$), 0.73 (C13-$C\underline{H}_3$), 0.95 and 0.85 (remaining methyl protons).

The U.V. spectrum of the compound, m.p. 96° exhibited absorption maximum at 247 nm which further supported 3-aza structure (CXI).



(CXIII)

Fig 2

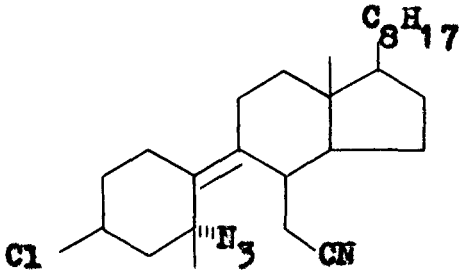
Characterization of the compound, m.p. 72° as 4-aza-A-homo-4a-ethylcholest-4a-eno[4,3-d]tetrazole (CXII)

The compound, m.p. 72° was analysed for $C_{29}H_{48}N_4$ which showed the presence of tetrazole moiety in the compound. The I.R. spectrum exhibited bands at 1630 (C=C), 1530, 1450, 1370 cm^{-1} (C=N, N=N). The N.M.R. spectrum of (CXII)(Fig. 2) was almost clean in the downfield region. The signal observed at δ 2.89 integrating for two protons is ascribable to $\underline{H}_2C2-C=N-$. Methyl protons were seen at δ 1.18 ($C10-C\underline{H}_3$), 0.68 ($C13-C\underline{H}_3$), 0.90 and 0.90 (remaining methyl protons).

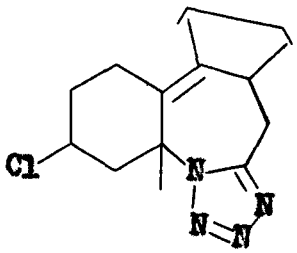
Its U.V. spectrum was found to be featureless in the region 220-360 nm. On the basis of molecular composition and spectral evidences the compound, m.p. 72° is characterized as 4-aza-A-homo-4a-ethylcholest-4a-eno[4,3-d]tetrazole (CXII).

Reaction of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (CI) with excess of hydrazoic acid

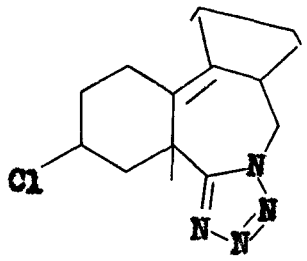
The ketone (CI) was treated with excess of hydrazoic acid in similar manner. After usual work up of reaction mixture and column chromatography over silica gel, two compounds; a non crystallizable oil (major) and a solid, m.p. 151° were separated in pure form.



(CXIII)



(CXIV)



(CXV)

Characterization of the oil, as 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (CXIII)

The oily compound was analysed for $C_{27}H_{43}N_4Cl$ (Positive Beilstein Test). In its I.R. spectrum bands at 2245 and 2100 cm^{-1} indicated the presence of nitrile and azido functions respectively. This often results as product of reaction with a ketone adjacent to a tetrasubstituted carbon. Its N.M.R. spectrum gave a broad multiplet centred at δ 4.2 integrating for one proton with $W_{\frac{1}{2}}$ = 16 Hz ascribable to C3-αH (axial). A sharp singlet at δ 1.65 integrating for 3 protons can be assigned to C5-methyl protons. The other methyl signals were observed at δ 0.68 (C13-CH_3), 0.90 and 0.91 (remaining methyl protons).

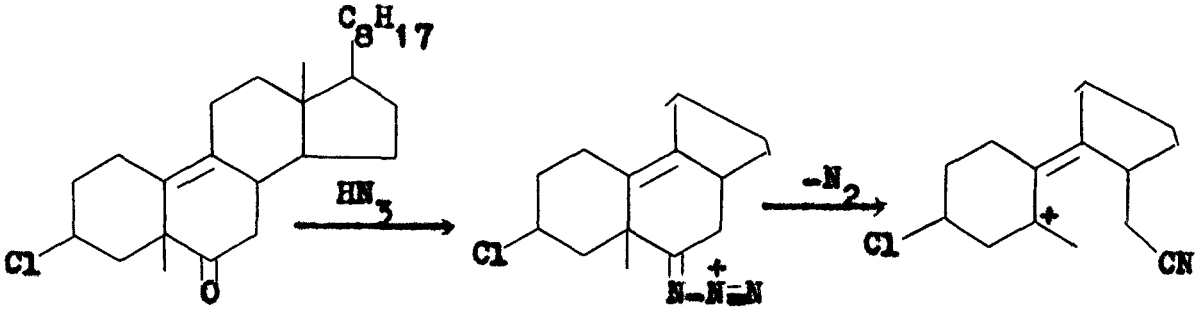
Characterization of the compound, m.p. 151° as 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno[6,7-d]tetrazole (CXIV)

The compound, m.p. 151° was analyzed for $C_{27}H_{43}N_4Cl$ (positive Beilstein Test). Its I.R. spectrum showed peaks at 1500, 1455 and 1370 cm^{-1}(C=N, N=N). A band at 760 cm^{-1} (C-Cl) can be assigned to axially substituted chlorine[24] at C3. N.M.R. spectrum of the compound m.p. 151° exhibited a broad multiplet centred at δ 3.83 integrating for one proton which is ascribable to C3-αH ($W\frac{1}{2}$ = 12 Hz; equatorial). The distinction between the possible isomeric structures (CXIV) and (CXV) was based upon the signal for C7a-protons. Since in the N.M.R. spectrum no signal was observed in the region δ 4-5 for methylene protons adjacent to nitrogen as in (CXV), therefore structure (CXV) is discarded. A signal at δ 3.45 integrating for one proton was assigned to C7a-H. It has been previously observed[10] that in N.M.R. spectrum of tetrazole (XXXII) only one of the C7a-protons appeared around δ 3.4 as the other one remains uninfluenced by the electron withdrawing nature of tetrazole ring and gets merged with the methylene envelop. Further C7a-H which is pseudo axial in nature has got a dihedral angle of about 90° with the axial C8-βH. For this reason there is no vicinal coupling and the C7a-H (pseudo axial) is geminally coupled with the other C7a-H to a magnitude of J=15 Hz. However, in this spectrum C7a-H(axial like) interestingly does not appear as a clean doublet. It is seen that this doublet which has a J value of 16 Hz is further splitted and the J values between the two parts of the each doublet is 6 Hz. This difference in splitting seems due to the different ring junction (cis) and presence of C9-C10 double bond in (CXIV). Interestingly

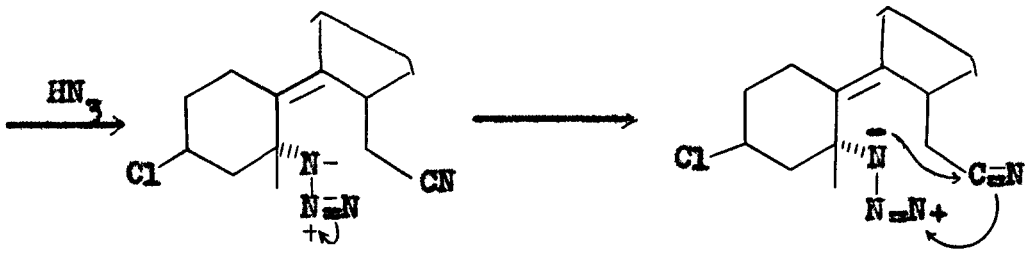
the signal for C13-methyl protons resonates at normal position (0.65) in (CXIV) in comparison to (XXXII) which showed a remarkable diamagnetic shift . It appears that the introduction of C9-C10 double bond and ring junction (cis) in (CXIV) alter the position of C13-methyl protons. The C5-βCH_3 was observed at δ 1.91 and other methyl signals were centred at 0.83, 0.75 and 0.65.

The intermediacy of (CXIII) during the course of formation of (CXIV) from (CI) was experimentally substantiated when oil (CXIII) was heated for 15 min which underwent cyclization to the chloro tetrazole and was found identical in all respects with (CXIV), isolated directly from reaction mixture.

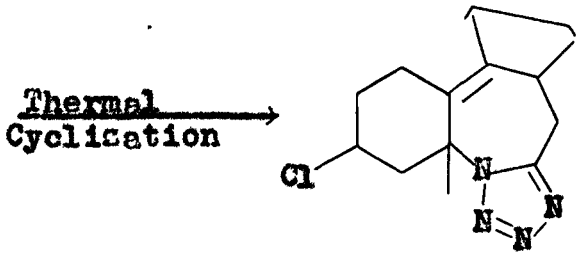
This novel cleavage of 6-oxosteroid to azido nitrile and its subsequent cyclization to tetrazole, finds analogy with the mechanism through which 17-oxosteroid is shown to undergo cleavage to azide nitrile which on thermal cyclization afforded tetrazole.[16,17] Following reaction sequence depicts the stages through which 6-oxosteroid (CI) is converted to (CXIV).



(CI) (a) (b)



(c) (CXIII)



(CXIV)

EXPERIMENTAL

Reaction of 4,4-dimethylcholest-5-en-3-one (XCVI) with hydrazoic acid-BF_3 etherate: 4,4-dimethyl-5α-cholestane-3,6-dione (CII) and 4-aza-A-homo-4a,4a-dimethylcholest-5-eno [3,4-d] tetrazole (CIII)

To a solution of (XCVI)(2 g) in benzene (25 ml) at 0-5° was added excess of hydrazoic acid and freshly distilled BF_3-etherate (2 ml) over a period of 5 hrs. The reaction mixture was left at room temperature for 3 days. After the reaction was complete, it was washed with sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oily residue (ca ~1.8 g) which was chromatographed on silica gel (40 g). Elution with light petroleum:ether (16:1) provided the compound (CII)(0.07 g), recrystallized from light petroleum m.p. 168°.

Analysis. Found: C, 81.30; H, 11.21.

$C_{29}H_{48}O_2$ requires : C, 81.28; H, 10.98%.

I.R. ν max 1700 cm^{-1} (C=O).

N.M.R. δ 2.2 mc (α-keto methylene protons), 1.12 (C10-$\underline{CH}_3$), 0.76 (C13-$\underline{CH}_3$), 0.95 and 0.85 (remaining methyl protons).

Further elution with light petroleum:ether (14:1) furnished solid compound (CIII) which was recrystallized from light petroleum (0.2 g), m.p. 132°.

Analysis. Found: C, 76.40; H, 10.72; N, 12.47.

$C_{29}H_{48}N_4$ requires: C, 76.99; H, 10.61; N, 12.47%.

I.R. ν max. 1640 (C=C), 1510, 1460 and 1375 cm^{-1} (C=N, N=N).

N.M.R. δ 6.17 (C6-$\underline{H}$), 3.16 mc (C2-$\underline{H}_2$), 1.94 and 1.82 (C4a-α-$C\underline{H}_3$ and β $C\underline{H}_3$), 1.16 (C10-$C\underline{H}_3$), 0.67 (C13-$C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

Reaction of 4-methylcholest-4-en-3-one (XCVIII) with hydrazoic acid-BF_3 etherate: 3-aza-A-homo-4a-methylcholest-4a-en-4-one (CVI) and 3-aza-A-homo-4a-methylcholest-4a-eno[3,4-d]tetrazole (CVII)

The solution of ketone (XCVIII)(2 g) in benzene (25 ml) was treated with excess of hydrazoic acid -BF_3 etherate in the manner described earlier. The residue obtained after usual work up of the reaction mixture was chromatographed over a column of silica gel (40 g). Elution with light petroleum:ether (9:1) provided a non crystallizable oil (CVI) (ca 0.06 g).

Analysis. Found: C,81.40; H,11.32; N,3.29.

$C_{29}H_{47}NO$ requires: C,81.35; H,11.38; N,3.38%.

I.R. ν max 3400 (NH), 1650 (C$\underline{O}$-NH), 1635 cm^{-1} (C=C).

N.M.R. δ 6.27s (N$\underline{H}$), 3.6br (C2-$\underline{H}_2$), 2.25s (C4a-$C\underline{H}_3$), 1.21(C10-$C\underline{H}_3$), 0.72 (C13-$C\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons).

Further elution with light petroleum:benzene (3:4) afforded a solid compound (CVII) recrystallized from ethyl alcohol (0.25 g), m.p. 141°.

Analysis. Found: C,76.30; H,10.56; N,12.85.

$C_{28}H_{46}N_4$ requires: C,76.71; H,10.50; N,12.78%.

I.R. ν max 1600 (C=C), 1510, 1450, 1375 cm^{-1} (C=N, N=N).

N.M.R. δ 4.35 mc (C2-$\underline{H}_2$), 2.31s (C4a-$C\underline{H}_3$), 1.22 (C10-$C\underline{H}_3$), 0.72 (C13-$C\underline{H}_3$), 0.9 and 0.88 (remaining methyl protons).

Reaction of 4,4-diethylcholest-5-en-3-one (XCIX) with hydrazoic acid-BF_3 etherate:4,4-diethyl-3,4-seco-4β-azidocholest-5-en-3-nitrile (CVIII) and 4-aza-A-homo-4a,4a-diethylcholest-5-eno [4,3-d] tetrazole (CIX)

A solution of ketone (XCIX)(2 g) in benzene (25 ml) was treated with excess of hydrazoic acid-BF_3 etherate in the usual manner. After the completion of reaction, the reaction mixture was worked up and the residue obtained was chromatographed over a column of silica gel (40 g). Elution with light petroleum:ether (9:1) gave (CVIII) as a non-crystallizable oil (ca 0.23 g).

Analysis. Found: C,77.5; H,10.83; N,11.66.

$C_{31}H_{52}N_4$ requires: C,77.5; H,10.83; N,11.66%.

I.R. ν max 2240 (-CN), 2100 ($-N_3$), 1630 cm^{-1} (C=C).

N.M.R. δ 5.28 mc (C6-$\underline{H}$), 1.08 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons).

Further elution with light petroleum:ether (2:1) provided a solid which on recrystallization from ethyl alcohol gave (CIX) (0.69 g), m.p. 135°.

Analysis. Found: C,77.66; H,10.80; N,11.63.

$C_{31}H_{52}N_4$ requires: C,77.50; H,10.83; N,11.66%.

I.R. ν max 1635 (C=C), 1510, 1450, 1380 cm^{-1} (C=N, N=N).
N.M.R. δ 5.89 mc (C6-$\underline{H}$), 2.96 mc (C2-$\underline{H}_2$), 0.9 (C10-$C\underline{H}_3$), 0.67 (C13-$C\underline{H}_3$), 0.83 and 0.80 (remaining methyl protons).

Reaction of 4-ethylcholest-4-en-3-one (C) with hydrazoic acid-BF_3 etherate: 3-aza-4-homo-4a-ethylcholest-4a-eno[3,4-d] tetrazole (CXI) and 4-aza-4-homo-4a-ethylcholest-4a-eno[4,3-d] tetrazole (CXII)

The solution of ketone (C)(2 g) in benzene (25 ml) was treated with excess of hydrazoic acid-BF_3 etherate as described earlier. After the usual work up, the residue obtained was chromatographed over the column of silica gel (40 g). Elution with light petroleum:ether (7:1) provided a solid (CXI), recrystallized from light petroleum (0.43 g), m.p. 96°.

Analysis. Found: C, 77.0; H, 10.59; N, 12.35.
$C_{29}H_{48}N_4$ requires: C, 76.99; H, 10.62; N, 12.39%.

I.R. ν max 1600 (C=C), 1510, 1450, 1380 cm^{-1} (C=N, N=N).
N.M.R. δ 4.39 mc (C2-$\underline{H}_2$), 1.18 (C10-$C\underline{H}_3$), 0.73 (C13-$C\underline{H}_3$), 0.95 and 0.85 (remaining methyl protons).

Further elution with light petroleum (6:1) gave (CXII) which was recrystallized from light petroleum (0.39 g), m.p. 72°.

Analysis. Found: C, 77.12; H, 10.58; N, 12.36.
$C_{29}H_{48}N_4$ requires: C, 76.99; H, 10.62; N, 12.39%.

I.R. ν max 1630 (C=C), 1530, 1450, 1380 cm^{-1} (C=N, N=N).

N.M.R. δ 2.89 mc ($C2-\underline{H}_2$), 1.18 ($C10-C\underline{H}_3$), 0.68 ($C13-C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

Reaction of 3β-chloro-19-nor-5-methyl-5β-cholest-9(10)-en-6-one (CI) with hydrazoic acid-BF_3 etherate: 3β-chloro-5,6-seco-19-nor-5α-azido-5β-methylcholest-9(10)-en-6-nitrile (CXIII) and 3β-chloro-6-aza-B-homo-19-nor-5-methyl-5β-cholest-9(10)-eno [6,7-d] tetrazole (CXIV)

The ketone (CI)(2 g) was treated with hydrazoic acid-BF_3 etherate. After the completion of the reaction, the reaction mixture was worked up to obtain the residue which was chromatographed over the column of silica gel (40 g). Elution with light petroleum:ether (19:1) provided an oily product (CXIII)(ca ~ 0.25 g).

Analysis. Found: C, 70.64; H, 10.11; N, 12.34.

$C_{27}H_{43}N_4Cl$ requires: C, 70.74; H, 9.38; N, 12.22%.

I.R. ν max 2245 (-CN), 2100($-N_3$), 760 cm^{-1} (C-Cl).

N.M.R. δ 4.2 ($C3-\alpha\underline{H}$), 1.65 ($C5-C\underline{H}_3$), 0.68 ($C13-C\underline{H}_3$), 0.9 and 0.8 (remaining methyl protons).

Further elution with chloroform yielded a solid compound (CXIV), recrystallized from ethyl alcohol (0.4 g), m.p. 151°.

Analysis. Found: C, 70.53; H, 9.41; N, 12.32.

$C_{27}H_{43}N_4Cl$ requires: C, 70.74; H, 9.38; N, 12.22%.

I.R. ν max 1500, 1455, 1370 (C=N, N=N), 760 cm^{-1} (C-Cl).

N.M.R. δ 3.39 ($C3-\alpha\underline{H}$; $W\frac{1}{2}$ = 12 Hz), 3.45 ($C7a-\underline{H}$), 1.81 ($C5-C\underline{H}_3$), 0.65 ($C13-C\underline{H}_3$), 0.88 and 0.75 (remaining methyl protons).

Thermal cyclization of (CXIII) to (CXIV)

The oil (CXIII)(ca ~ 0.1 g) was heated at 225° for 15 min, which yielded the compound (CXIV)(0.06 g), m.p. 151° crystallized from ethylalcohol. It was found identical with (CXIV).

REFERENCES

1. J.A. Bladin, Ber., 18, 1544, 2907 (1885).

2. J.A. Bladin, Ber., 19, 2598 (1886).

3. F.R. Benson, "Heterocyclic Compounds", Vol. 8, Edited by R.C. Elderfield (John Wiley and Sons, Inc. New York), p.1-104(1

4. Beckmann, "Pharmacology", 2nd. Ed., Saunders, Philadelphia, 1961, p. 318-23.

5. K.F. Schmidt, Ber., 57, 704 (1924).

6. P.A.S. Smith, J. Am. Chem. Soc., 70, 320 (1948).

7. C.S. Barnes, D.H.R. Barton, J.S. Fawcett and B.R. Thomas, J. Chem. Soc., 2339 (1952).

8. R. Mechoulam, Israel J. Chem., 6, 909 (1968).

9. A. Cervantes, P. Crabbe, J. Iriarte and G. Rosenkranz, J. Org. Chem., 33, 4294 (1968).

10. M.S. Ahmad and I.A. Khan, Ind. J. Chem., 15B, 1016 (1977).

11. M.S. Ahmad, Z.H. Choudhry and P.N. Khan, Aust. J. Chem., 29, 447 (1976).

12. H. Singh, T.R. Bhardwaj and D. Paul, J. Chem. Soc., (Perkin-Trans I) 18, 1987 (1977).

13. H. Singh, K.K. Bhutani, R.K. Malhotra and D. Paul, Experientia, 34(5), 557 (1978).

14. H. Singh, R.B. Mathur and P.P. Sharma, J. Chem. Soc., (Perkin-Trans I) 990 (1972).

15. M.S. Ahmad, S.R. Husain, M. Husain and Z.H. Choudhry, Ind. J. Chem., 16B, 559 (1978).

16. H. Singh, R.K. Malhotra and V.V.Parashar, Tetrahedron Letters, 2597 (1973).

17. H. Singh, R.K. Malhotra and V.V. Parashar, Ind. J. Chem., 13, 761 (1975).

18. H. Singh, R.K. Malhotra, A.S. Chawla and N.K. Luhadia, Ind. J. Chem., 14B, 618 (1976).

19. H. Singh and M.K. Biyani, Ind. J. Chem., 15B, 570 (1977).

20. H. Singh and T.R. Bhardwaj, Ind. J. Chem., 16B, 617 (1978).

21. J. Moural and K. Syhora, Coll. Czech. Chem. Commun, 35, 2019 (1970).

22. G. Just and Keith St. C. Richardson, Canad. J. Chem., 42, 456 (1964).

23. C.D. Nolo and V. Permutti, Tetrahedron, 22, 2059 (1966).

24. L.J. Bellamy, "The Infrared Spectra of Complex Molecules", (John Wiley, New York)(1958).

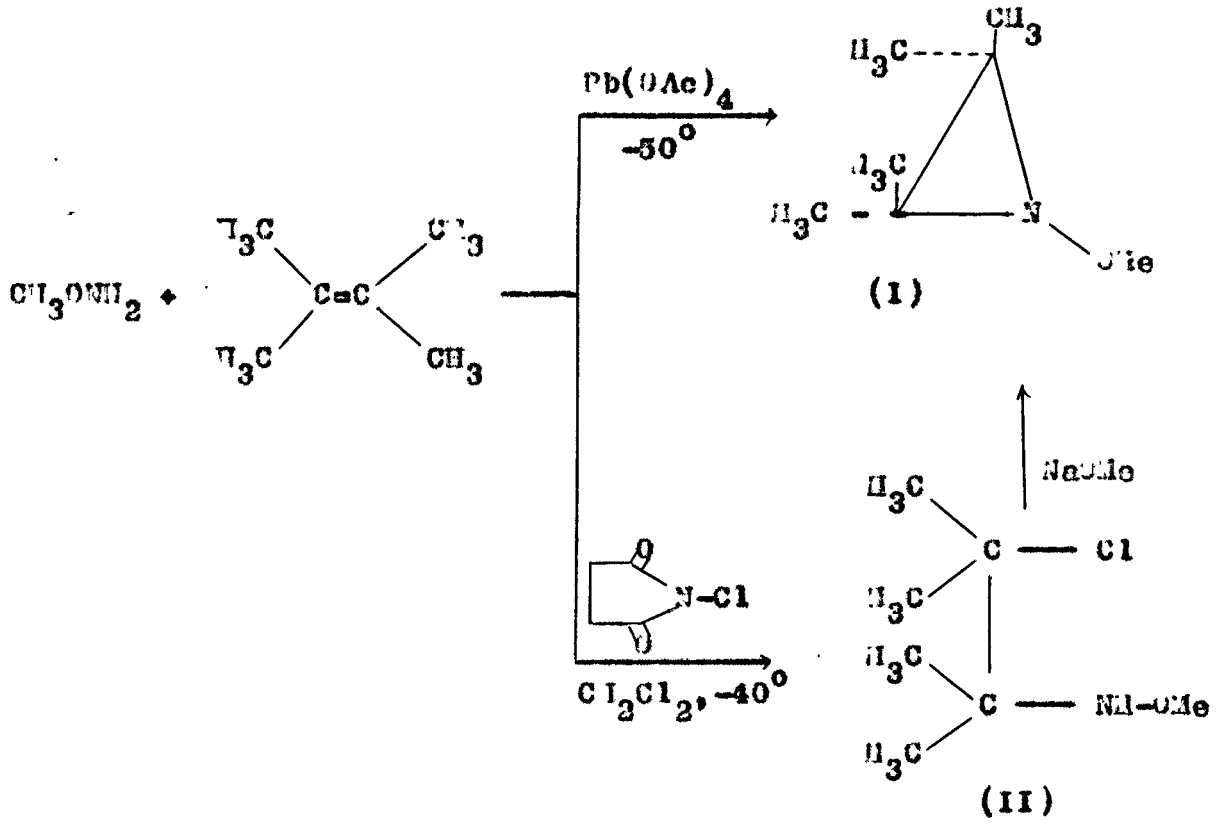
THEORETICAL

The Chemistry and stereochemistry of three membered ring with their highly compressed bond angles has long intrigued the organic chemists. These strained organic cyclic compounds have a propensity towards ring opening. In fact the ability of aziridinium salts to undergo facile ring opening by nucleophiles can be used to explain the action of aziridines and of related β-haloamines as carcinostats, possibly by alkylating enzyme sites. Thus "Fenesterin" an ester of cholesterol containing the β-haloamine moiety has been shown favourable carcinostatic activity in a number of tumor systems[1]. In connection with our work on stereospecific introduction of nitrogen containing functions into the steroid nucleus, we were interested in the synthesis of fused steroidal aziridines.

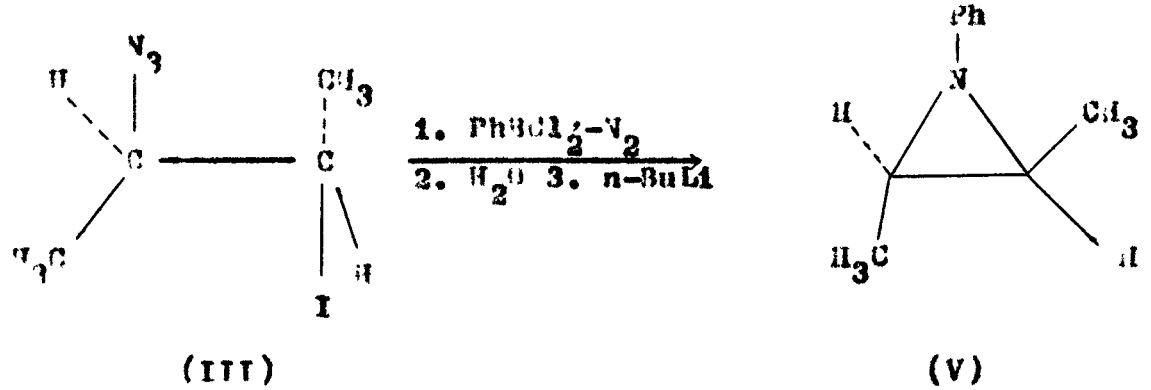
Synthesis of Aziridines

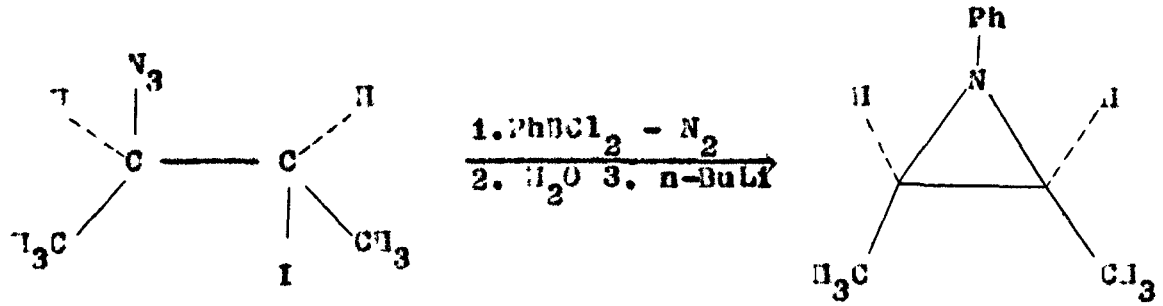
Several papers dealing with the synthesis of aziridines have appeared. The present chapter deals with some of the recent and pertinent examples of the aziridine preparations. Brois[2] oxidised methoxyamine with lead tetracetate in the presence of excess tetramethyl ethylene at -30° and obtained 1-methoxy-2, 2,3,3-tetra methylaziridine (I). When the reaction was repeated with N-chlorosuccinimide in methylene chloride at -40° hydroxyl-

amine (II) was obtained which on cyclization with sodium methoxide afforded the aziridine (I).



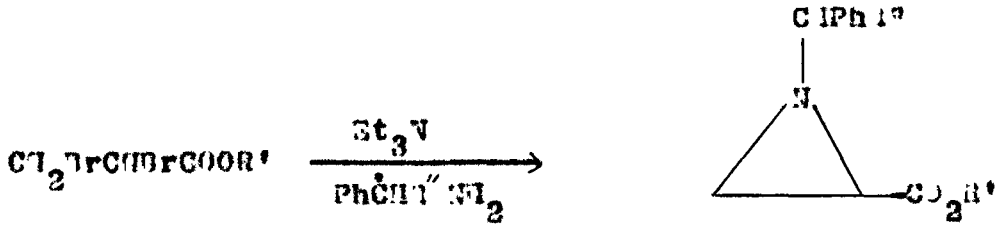
Levy et al.[3] reported the synthesis of N-Phenylaziridine (V) and (VI) from 1-azido-2-iodoethane (III) and (IV) as follows:





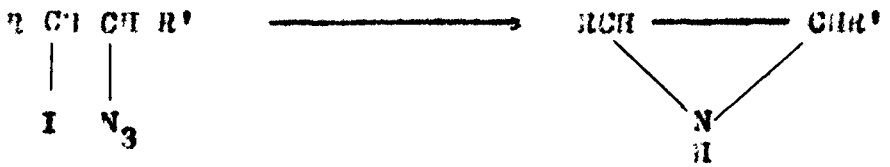
(IV) (VI)

Harada et al.[4] synthesized 1-alkylaziridine-2-carboxylates (VIIa-d) from the alkyl α,β-dibromopropionates in the presence of chiral benzylamine.



	R'	R''
(VII)-a	Me	Me or Et
-b	Et	,,
-c	Pr^i	,,
-d	Bu^t	,,

Wassner et al.[5] reported the synthesis of aziridines by selective reduction of the azide function followed by base catalysed ring closure (Table - 1).



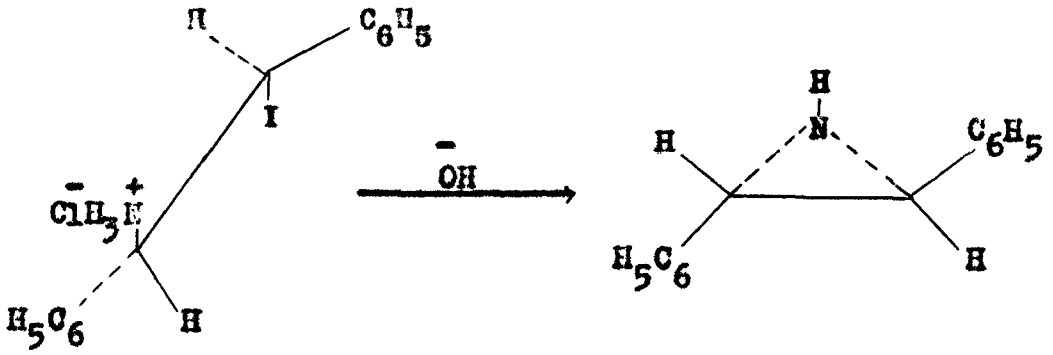
(VIII) (IX)

Table - I

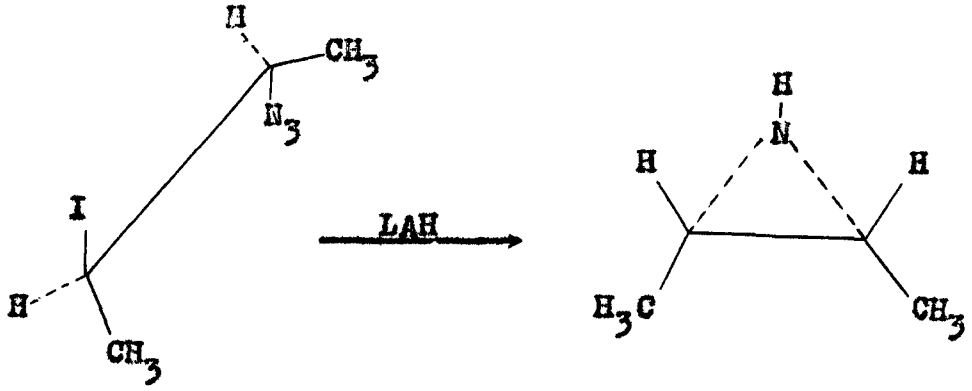
Reduction of 1,2-disubstituted 1-azido-2-iodoethanes with lithium aluminium hydride

Iodoazides		R	R'	% of aziridines	
(VIII)-a	(threo)	C_6H_5	C_6H_5	53 11	(cis) (trans)
-b	(erythro)	CH_3	CH_3	100	(cis)
-c	(threo)	CH_3	CH_3	100	(trans)
-d	(erythro)	C_2H_5	C_2H_5	100	(trans)
-e	(erythro)	i-pr	i-pr	95	(trans)
-f	(erythro)	C_6H_5	CH_3	95	(trans)
-g	(trans)	$(CH_2)_3$	$(CH_2)_3$	100	
-h	(trans)	$(CH_2)_4$	$(CH_2)_4$	100	
-i	(trans)	$(CH_2)_5$	$(CH_2)_5$	100	

Trans-diphenylaziridine (XI) was obtained by base catalysed hydrolysis of erythro-1-amino-2-iodo-1,2-diphenylethane hydrochloride (X), while threo-2-azido-3-iodobutane (XII) gave cis-2,3-dimethylaziridine (XIII)[5].

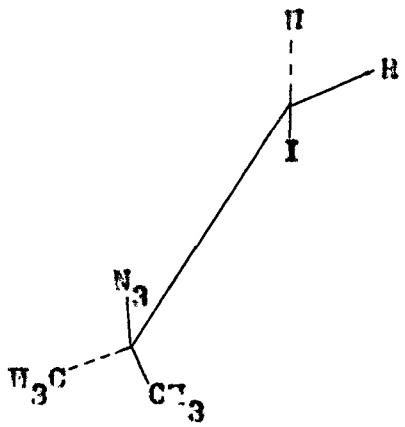


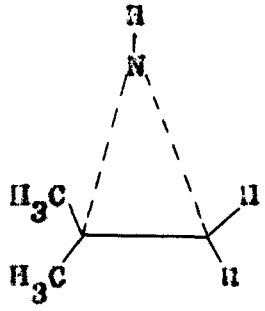
(X) (XI)



(XII) (XIII)

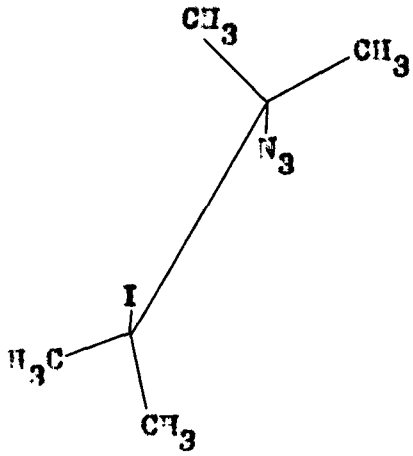
The trialkylethylene adducts (XIV) and (XV) gave 3-methyl and 3-ethyl-2,2-dimethylaziridines (XVI) and (XVII) under similar reaction conditions[5].

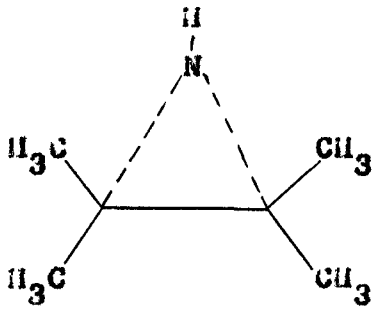




	R		R
(XIV)	CH_3	(XVI)	CH_3
(XV)	C_2H_5	(XVII)	C_2H_5

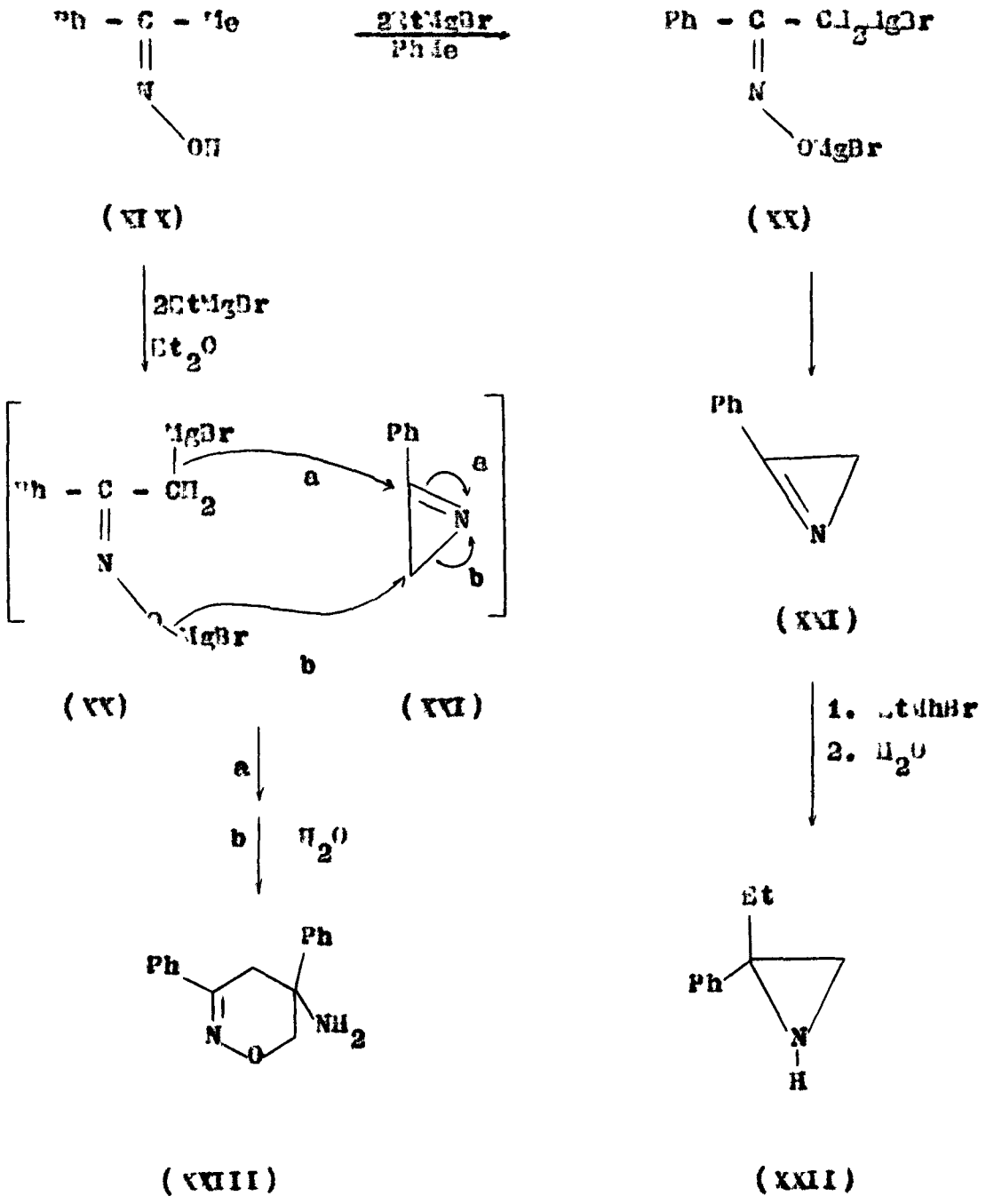
The iodoazide (XVII) on LAH reduction provided volatile 2,2,3,3-tetramethylaziridine (XVIII)[5].





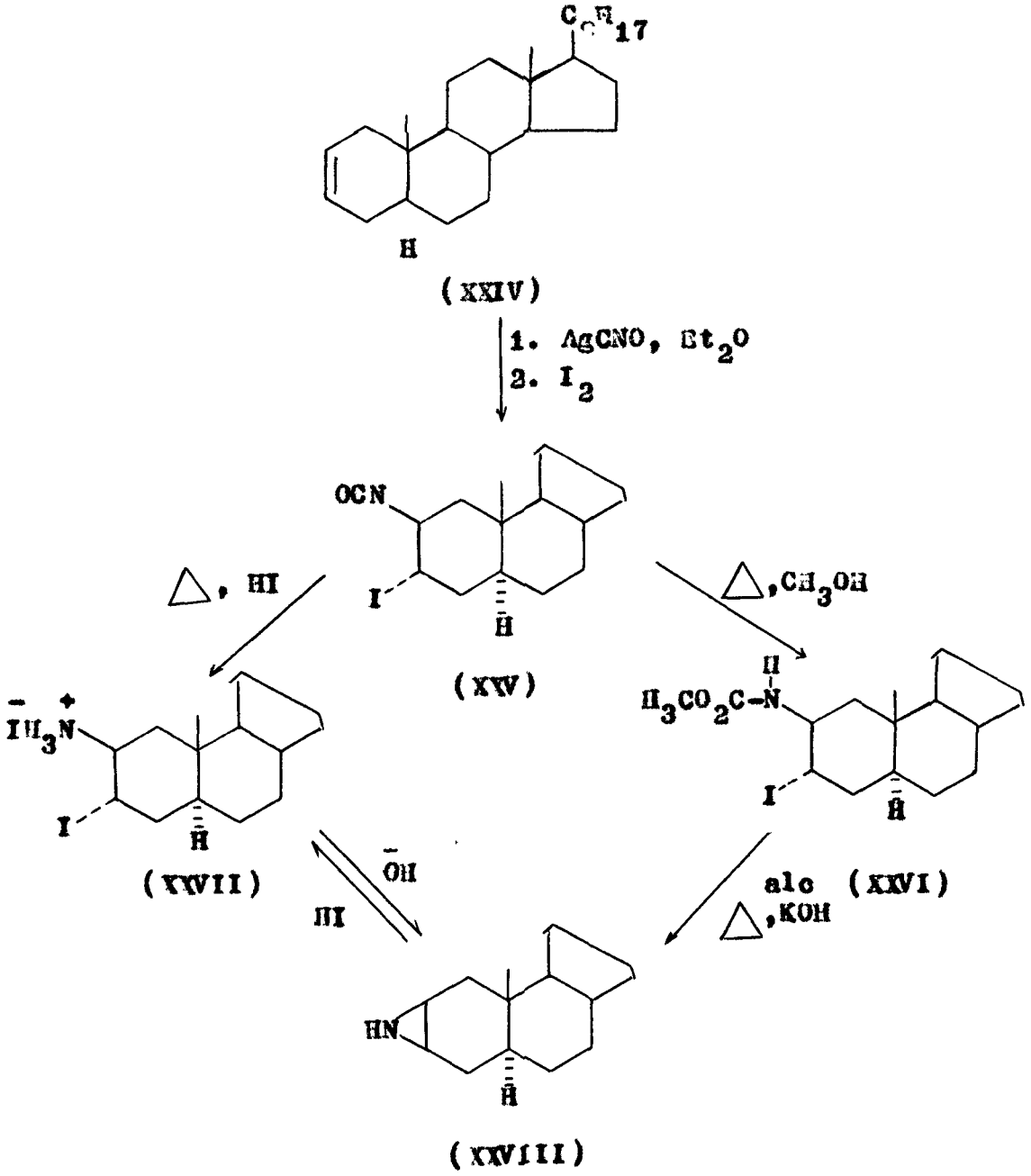
(XVII) (XVIII)

Recently Laurent et al.[6] reported the synthesis of secondary aziridines by the Hoch Compbell reaction (from an oxime with a Grignard reagent in toluene) which has found many applications and various cyclization mechanism has been proposed. However, the nature of the intermediates has not been established.

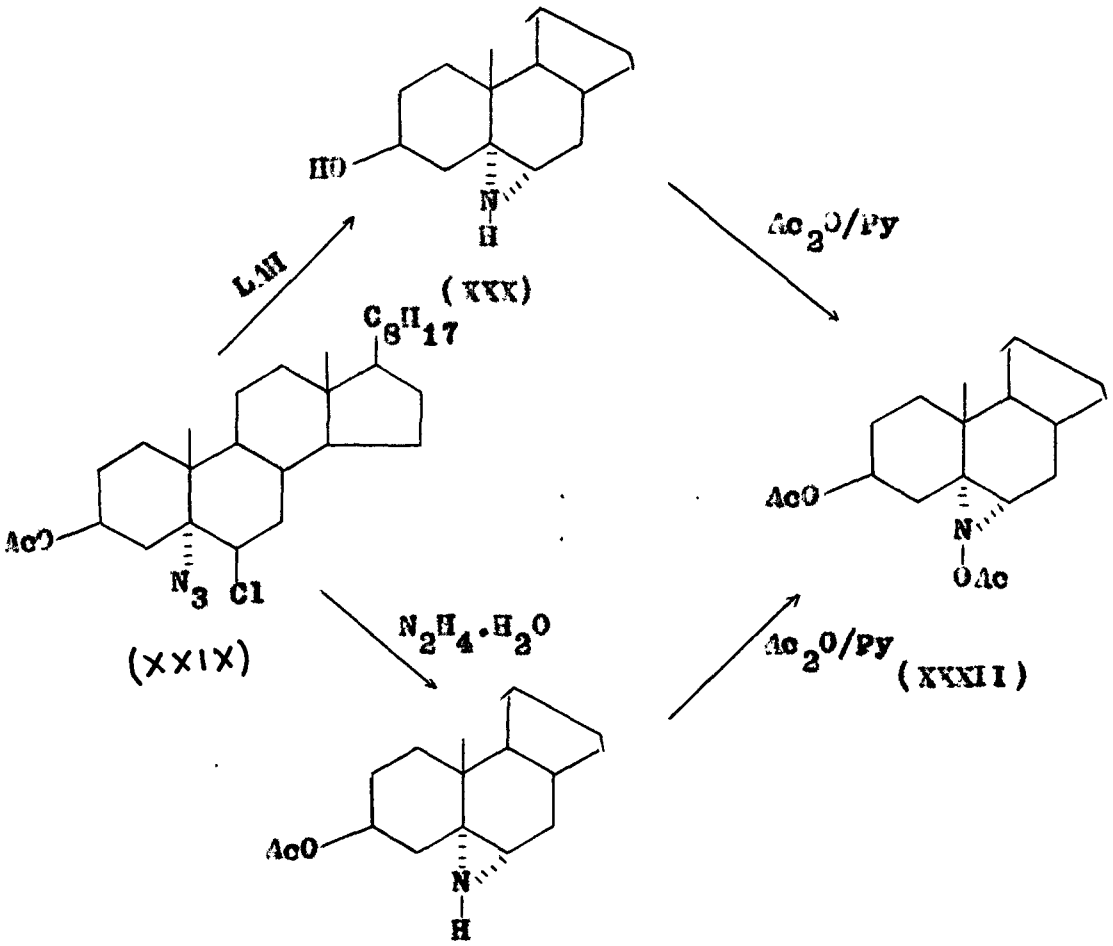


Steroidal Aziridines

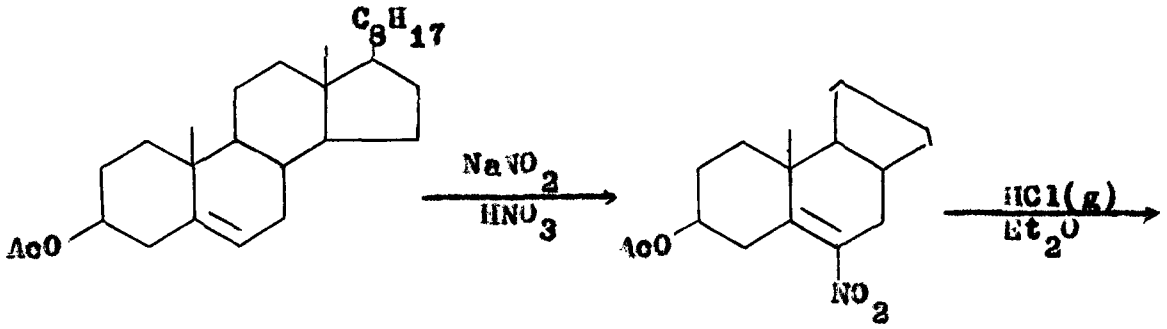
Hassner et al.[7] reported the synthesis of steroidal aziridines (XXVIII) according to scheme given below.



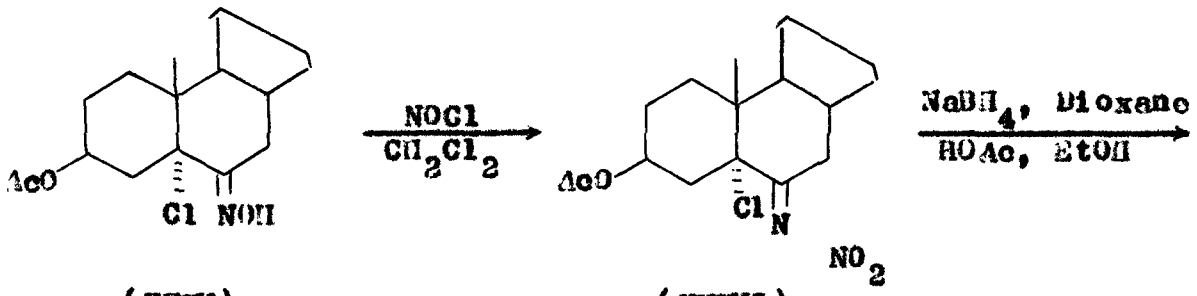
Snatzke et al.[8] prepared N-acetoxyaziridine (XXXII) from (XXIX) according to reaction sequence given below.



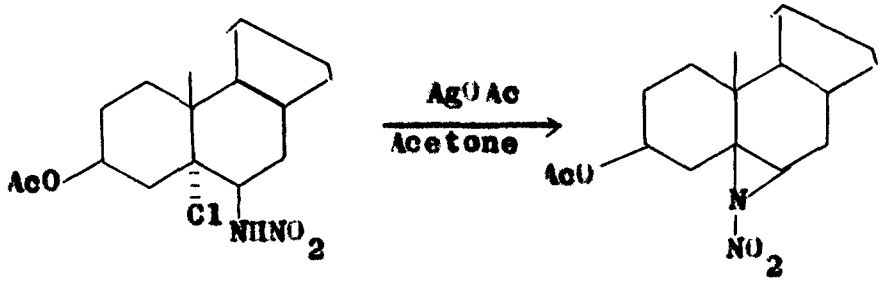
Naire et al.[9] reported the formation of N-nitroaziridine (XXXVIII) starting from 3β-acetoxycholest-5-ene (XXXIII).



(XXXIII) (XXXIV)

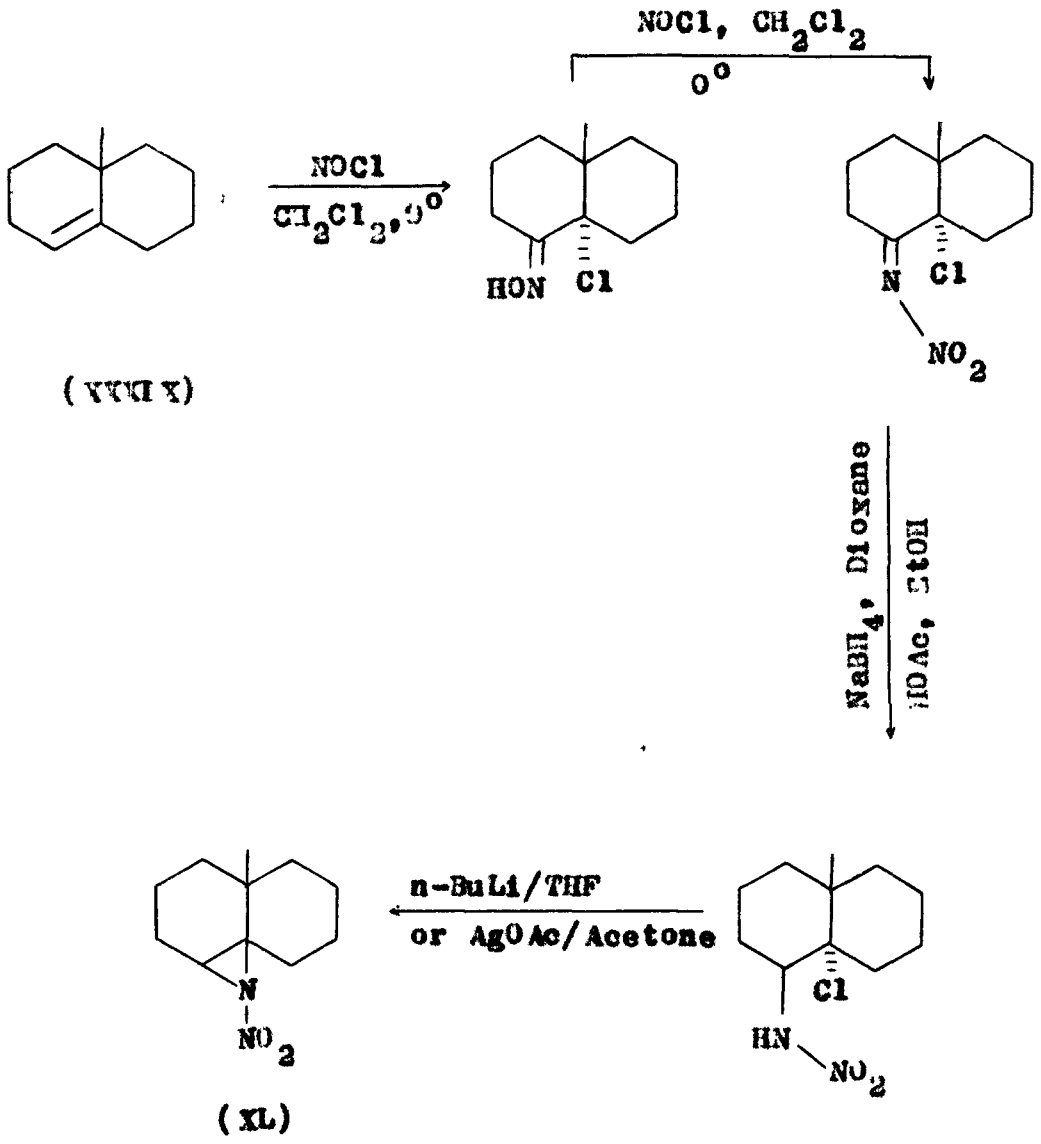


(XXXV) (XXXVI)



(XXXVII) (XXXVIII)

Similarly 10-methyl- $\Delta^{1,9}$-octalin (XXXIX) provided 10-methyl-1,9-(N-nitroaziridino) decalin (XL).



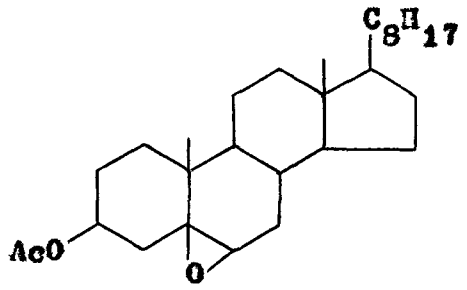
(XXXIX)

(XL)

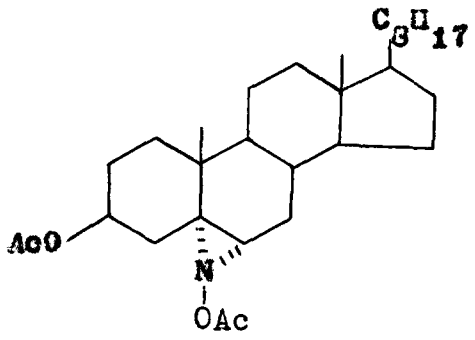
DISCUSSION

Among organic compounds which were found to show some degree of carcinostatic activity, the aziridine (or the related β-haloethylamine) functional grouping has maintained an outstanding place.

Fuchter et al.[10] synthesized the α-aziridine (XLII) from the β-epoxide (XLI) via Ritter reaction.

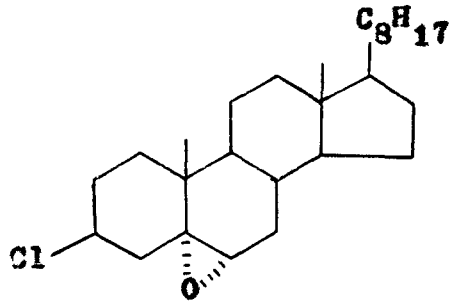


(XLI)

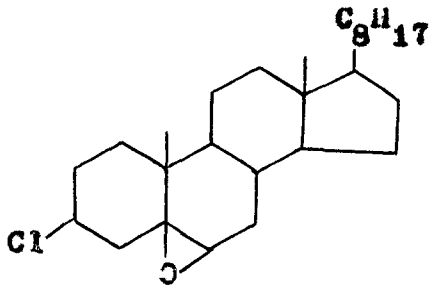


(XLII)

The present work describes the synthesis of aziridines derived from hitherto unexplored steroidal epoxides such as 3β-chloro-5,6α-epoxy-5α-cholestane (XLIII) and 3β-chloro-5,6β-epoxy-5β-cholestane (XLIV).



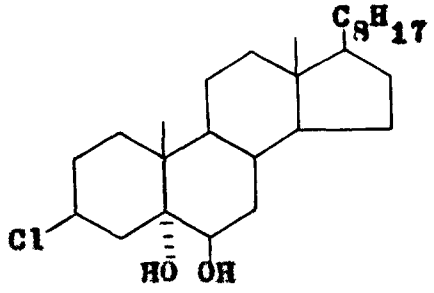
(XLIII)



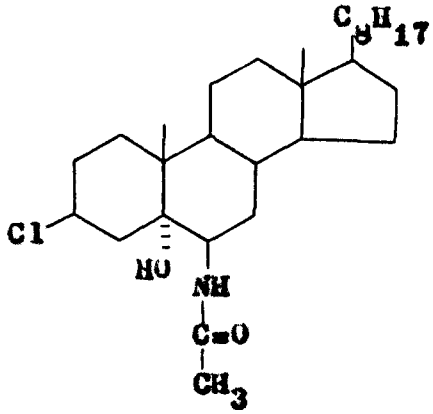
(XLIV)

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (XLIII) with acetonitrile-boron trifluoride etherate

Boron trifluoride etherate (as a catalyst) was added dropwise over a period of 15 min to a stirred suspension of 3β-chloro-5,6α-epoxy-5α-cholestane (XLIII) in acetonitrile at room temperature. After usual work up of the reaction mixture, the residue obtained was chromatographed over silica gel. Two solid compounds having m.p. 125° and 174° were obtained.



(XLV)



(XLVI)

Characterization of the compound, m.p. 125° as 3β-chloro-5,6β-dihydroxy-5α-cholestane (XLV)

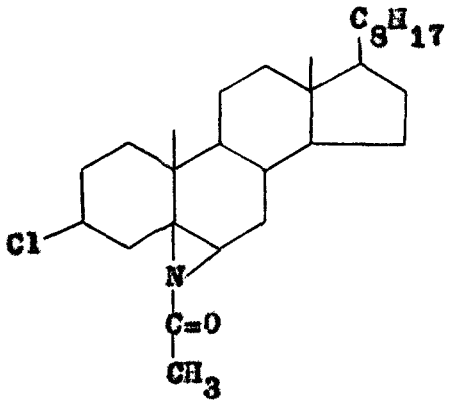
The compound, m.p. 125° (reported[11] m.p. 125-126°) was correctly analysed for $C_{27}H_{47}O_2Cl$. The molecular composition showed the addition of one oxygen atom to the substrate (XLIII). The I.R. spectrum exhibited absorption bands at 3420 (OH) and 760 cm^{-1} (C-Cl). No other bands were appeared. The compound was found identical with the authentic sample (t.l.c., i.r.).

Characterization of the compound, m.p. 174° as 3β-chloro-5-hydroxy-6β-acetylamino-5α-cholestane (XLVI)

The compound, m.p. 174° was analysed for $C_{29}H_{50}NO_2Cl$. The I.R. spectrum showed bands at 3405 (OH), 3410 (NH), 1670 (amide I), 1500 (amide II), 760 cm^{-1} (C-Cl). In N.M.R. spectrum a broad signal revealed at δ 4.23 ($W_{\frac{1}{2}}$ = 16 Hz) integrating for one proton is ascribable to (C3-$\underline{H}$; axial). The half band width showed that the ring junction is trans. A doublet at δ 3.62 (J=10 Hz; disappeared on addition of D_2O) integrating for one proton is assigned to C6-$\underline{NH}$-CO- and a multiplet centred at δ 2.74 to C6-$\underline{H}$. Methyl signals were obtained at δ 2.0s(-NH-CO-$\underline{CH_3}$), 1.13 (C10-$\underline{CH_3}$), 0.69 (C13-$\underline{CH_3}$), 0.89 and 0.90 (remaining methyl protons). On the basis of above elemental analysis and spectral evidences the compound (XLVI) is characterized as 3β-chloro-5-hydroxy-6β-acetylamino-5α-cholestane.

Treatment of 3β-chloro-5-hydroxy-6β-acetylamino-5α-cholestane (XLVI) with alcoholic sodium hydroxide

The compound (XLVI) was refluxed with alcoholic sodium hydroxide (10%). The reaction mixture after usual work up provided a fine crystalline solid, m.p. 100°.

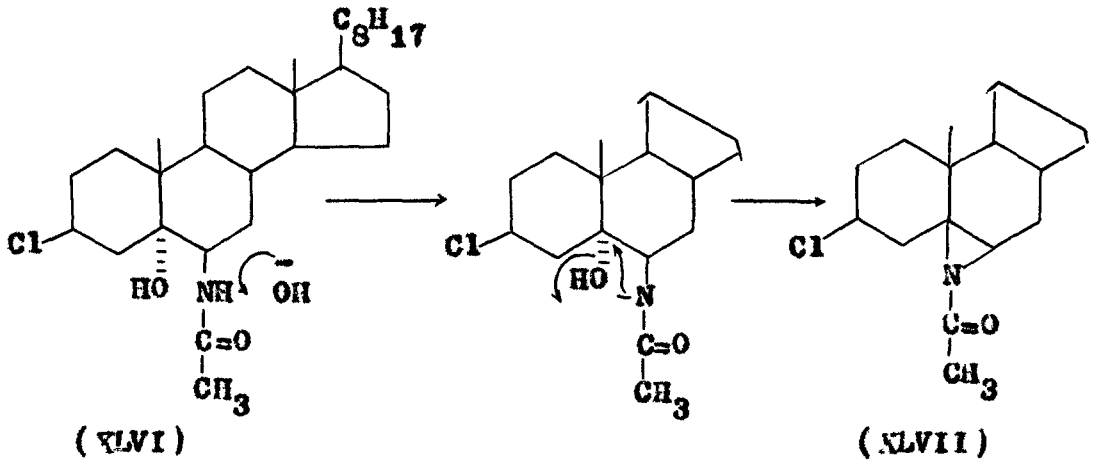


(XLVII)

Characterization of the compound, m.p. 160° as 1'-Acetyl-3β-chloro-5β-cholestano[5,6-b]azirine (XLVII)

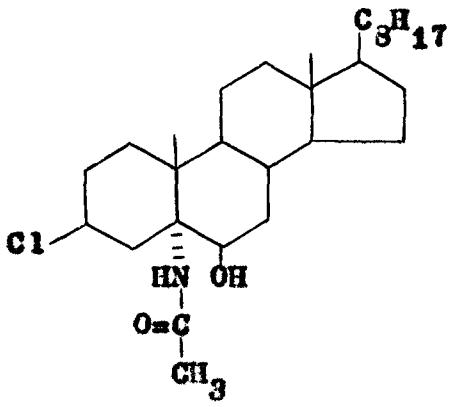
The compound, m.p. 160° showed the molecular composition $C_{29}H_{48}ONCl$. Bands observed in I.R. spectrum were 1660 (amide III), 765 cm^{-1} (C-Cl). In N.M.R. spectrum a broad signal exhibited at δ 3.76 ($W_{\frac{1}{2}}$ = 9 Hz) integrating for one proton is assigned to C3-αH. The half band width showed that the C3-proton is equatorially oriented and ring junction is cis i.e. azirine ring is β-oriented. C6-αH appeared at δ 2.87 as multiplet in

N.m.r. spectrum. Methyl signals were observed at δ 2.0s ($\rangle$N-CO-C$\underline{H}_3$), 1.04 (C10-C$\underline{H}_3$), 0.73 (C13-C$\underline{H}_3$), 0.92 and 0.84 (remaining methyl protons). On the basis of above elemental and spectral data the compound (XLVII) is characterized as 1'-acetyl-3β-chloro-5β-cholestano[5,6-b]azirine. To account for the formation of (XLVII) the following mechanism is being proposed.



Reaction of 3β-chloro-5,6β-epoxy-5β-cholestane (XLIV) with acetonitrile-boron trifluoride etherate

Boron trifluoride etherate was added to a stirred ice cooled suspension of β -epoxide (XLIV) in acetonitrile until all the solid dissolved. The mixture was stirred at room temperature for 15 min. After usual work up and column chromatography over silica gel, diol (XLV) and a compound, m.p. 267^{o} were obtained.



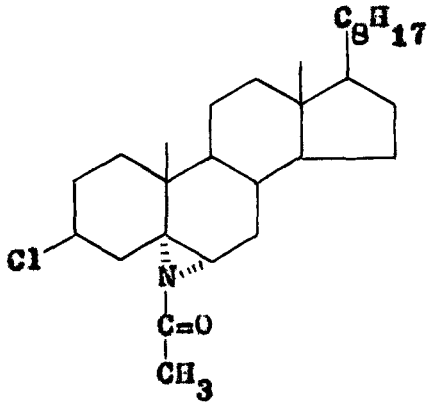
(XLVIII)

Characterization of the compound, m.p. 267° as 3 -chloro-5-acetylamino-6 -hydroxy-5 -cholestane (XLVIII)

The compound, m.p. 267° was analysed for $C_{29}H_{50}NO_2Cl$. The I.R. spectrum exhibited bands at 3400 (OH), 3390 (NH), 1665 (amide I), 1490 (amide II), 765 cm^{-1} (C-Cl). In N.M.R. spectrum a broad signal appeared at δ 3.87 ($W\frac{1}{2}$ = 15 Hz) integrating for one proton is ascribable to C3-$\underline{\alpha}$H (axial; A/B trans). A broad singlet at δ 5.2 is assigned to C3-N$\underline{H}$-CO. A multiplet centred at δ 3.08 integrating for one proton is ascribable to C6-$\underline{\alpha}$H. The methyl signals were observed at δ 2.02s (NH-CO-C$\underline{H}_3$), 1.4 (C10-C$\underline{H}_3$), 0.73 (C13-C$\underline{H}_3$), 0.93 and 0.86 (remaining methyl protons). These values are compatible with the structure given to compound (XLVIII).

Treatment of 3β-chloro-5-acetylamino-6β-hydroxy-5α-cholestane (XLVIII) with alcoholic sodium hydroxide

Compound (XLVIII) was refluxed with alcoholic sodium hydroxide (10%). After usual work up and column chromatography over silica gel a non-crystallizable oil was obtained.



(XLIX)

Characterization of oil as 1'-Acetyl-3β-chloro-5β-cholestano [5,6-b]azirine (XLIX)

The compound (XLIX) was analysed for $C_{29}H_{49}ONCl$ and its I.R. spectrum showed a characteristic peak at 1665 cm^{-1} (amide III) for azirine and other peak at 775 cm^{-1} (C-Cl). The N.M.R. spectrum revealed a broad signal at δ 4.37 integrating for one proton is ascribable to C3-$\underline{\alpha}$H ($W_{\frac{1}{2}}$ = 14 Hz; axial; A/B trans; azirine ring α-oriented). A multiplet centred at δ3.29 assigned to C6-$\underline{\beta}$H. Methyl signals were seen at δ 1.0s

(N-CO-$\underline{CH}_3$), 1.15 (C10-$\underline{CH}_3$), 0.68 (C13-$\underline{CH}_3$), 0.93 and 0.85 (remaining methyl protons). On the basis of above elemental analysis and spectral data the compound (XLIX) is characterised as 1'-acetyl-3β-chloro-5α-cholestano[5,6-b]azirine.

EXPERIMENTAL

3β-Chloro-5,6α-epoxy-5α-cholestane (XLIII)

Cholesteryl chloride (11 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equivalent) in chloroform and left at -8° for 20 hrs. The mixture was then washed with ice-cold sodium bicarbonate solution (5%), water and sodium thiosulphate solution. Evaporation of the solvent yielde (XLIII)as an oil which was crystallized from acetone as needles (9.1 g), m.p. 89° (reported[11] m.p. 89.5-90.5°).

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (XLIII) with acetonitrile-BF_3-etherate: 3β-Chloro-5,6β-dihydroxy-5α-cholestane (XLV) and 3β-chloro-5-hydroxy-6β-acetylamino-5α-cholestane (XLVI)

Boron trifluoride-etherate (3.5 ml) was added dropwise over 15 min to a stirred suspension of α-epoxide (XLIII)(3.5 g) in acetonitrile (35 ml) at room temperature. The resulting solution was further stirred for 2 hrs and then diluted with water and extracted with ether. The organic layer was washed with sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil (ca ~2.6 g) which was chromatographed over silica gel (60 g). Elution with light petroleum:ether (9:1) gave the diol (XLV), recrystallized from light petroleum (0.3 g), m.p. and m.m.p. 125-26° (reported[11] m.p. 126°).

Further elution with light petroleum:ether (3:1) furnished (XLVI), recrystallized from light petroleum (1.59 g), m.p. 174°.

Analysis. Found: C, 72.67; H, 10.41; N, 2.95

$C_{29}H_{50}NO_2Cl$ requires: C, 72.63; H, 10.44; N, 2.92%.

I.R. ν max 3465 (OH), 3410 (NH), 1670 (amide I), 1500 (amide II), 760 cm^{-1} (C-Cl).

N.M.R. δ 5.62d (C6-$\underline{H}$-CO-; J = 10 Hz), 4.28br (C3-$\underline{H}$; $W\frac{1}{2}$ = 10 Hz; axial), 2.74 mc (C6-$\underline{H}$), 2.0s (NH-CO-$C\underline{H}_3$), 1.13 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.89 and 0.80 (remaining methyl protons).

Treatment of 3β-chloro-5-hydroxy-6β-acetylamino-5α-cholestane (XLVI) with alcoholic sodium hydroxide:1'-Acetyl-3β-chloro-5β-cholestano[5,6-b]azirine (XLVII)

Compound (XLVI)(1.0 g) was dissolved in ethanol and to this was added an alcoholic sodium hydroxide solution (10%; 15 ml). The reaction mixture was refluxed for 3 hrs and then acidified with HCl, and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. The oil thus obtained on evaporation of the solvent gave the compound (XLVII)(0.63 g), m.p. 160 on crystallization from light petroleum.

Analysis. Found: C, 75.45; H, 10.38; N, 2.98.

$C_{29}H_{48}ONCl$ requires: C, 75.48; H, 10.40; N, 3.0%.

I.R. ν max 1660 (amide III), 765 cm^{-1} (C-Cl).

N.M.R. δ 3.76br (C3-αH; $W\frac{1}{2}$ = 9 Hz, equatorial), 2.87 mc (C6-αH), 2.0s (-N-CO-CH_3), 1.04 (C10-CH_3), 0.73 (C13-CH_3), 0.92 and 0.84 (remaining methyl protons).

3β-Chloro-5-bromo-6β-acetoxy-5α-cholestane

Cholesteryl chloride (10 g) was dissolved in carbon tetrachloride (25 ml) and cooled to 0°. To this added acetyl hypobromite[12] (0.1M, 250 ml) at 0°. After 5 min the resultant solution was mixed with cold sodium bisulfite solution (5 ml; 10%). The organic layer was then washed with water, dried over anhydrous sodium sulphate. Removal of the solvent provided a residue (9.2 g) which was crystallized from methanol. Several crystallization from methanol afforded a fine crystal (8 g), m.p. 137-139°.

3β-Chloro-5,6β-epoxy-5β-cholestane (XLIV)

3β-Chloro-5-bromo-6β-acetoxy-5α-cholestane (3 g) was treated under reflux for 1 hr with methanolic sodium hydroxide solution (30 ml; 5%). The solution was cooled, neutralized with glacial acetic acid and excess of the solvent was removed under reduced pressure. Water (100 ml) was added. After usual work up procedure and subsequent removal of the solvent gave

crude product which was recrystallized from methanol to give (XLIV) (2 g), m.p. 84-86°.

Analysis. Found: C, 76.9; H, 10.5.

$C_{27}H_{45}OCl$ requires: C, 77.0; H, 10.8%.

I.R. ν max 860 (epoxide) and 765 cm^{-1} (C-Cl).

N.M.R. δ 3.71br (C3-$\underline{H}$; $W_{\frac{1}{2}}$ = 9 Hz; equatorial); 2.91d (C6-$\underline{H}$), 0.95 (C10-$C\underline{H}_3$), 0.61 (C13-$C\underline{H}_3$), 0.88 and 0.78 (remaining methyl protons).

Treatment of 3β-chloro-5,6β-epoxy-5β-cholestane (XLIV) with acetonitrile-BF_3-etherate: Diol (XLV) and 3β-chloro-5-acetylamino-6β-hydroxy-5α-cholestane (XLVIII)

β-Epoxide (XLIV)(3 g) was treated with acetonitrile (30 ml) and BF_3-etherate (3 ml) at room temperature for 15 min. The reaction mixture was worked up as described for (XLIII). The residue obtained after the removal of solvent was chromatographed over silica gel (60 g). Elution with light petroleum:ether (16:1) afforded the diol (XLV)(0.6 g), m.p. 125-26° (reported[11], m.p.126°).

Further elution with light petroleum:ether (4:1) gave (XLVIII) which was recrystallized from light petroleum (1.68 g), m.p. 267°.

Analysis. Found: C, 72.67; H, 10.41; N, 2.95.

$C_{29}H_{50}NO_2Cl$ requires: C, 72.65; H, 10.44; N, 2.92%.

I.R. ν max 3460 (OH), 3390 (NH), 1665 (amide I), 1490 (amide II), 765 cm^{-1} (C-Cl).

N.M.R. δ 3.87br (C3-αH; $W\frac{1}{2}$ = 15 Hz; axial), 3.08 mc (C6-αH), 5.2br,s (C5-αNH-CO-), 2.02s (-NH-CO-CH_3), 1.4 (C10-CH_3), 0.73 (C13-CH_3), 0.93 and 0.86 (remaining methyl protons).

Treatment of 3β-chloro-5-acetylamino-6β-hydroxy-5α-cholestane (XLVIII) with alcoholic sodium hydroxide: 1'-Acetyl-3β-chloro-5α-cholestano[5,6-b]azirine (XLIX)

Compound (XLVIII)(1.0 g) dissolved in ethanol was mixed with alcoholic sodium hydroxide (10%; 15 ml). The reaction mixture was refluxed for 3 hrs then it was acidified with HCl and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate anhydrous. On evaporation of the solvent, the compound (XLIX)(ca 0.7 g) was obtained as non crystallizable oil.

Analysis. Found: C, 75.45; H, 10.38; N, 2.98.

$C_{29}H_{48}ONCl$ requires: C, 75.48; H, 10.40; N, 3.0%.

I.R. ν max 1665 (amide III), 775 cm^{-1} (C-Cl).

N.M.R. δ 4.37 br (C3-αH; $W\frac{1}{2}$ = 14 Hz; axial), 3.28 mc (C6-βH), 1.9s (N-CO-CH_3), 1.15 (C10-CH_3), 0.68 (C13-CH_3), 0.93 and 0.85 (remaining methyl protons).

REFERENCES

1. International cancer congress, Moscow, 1962; See. S.A. Dyogteva, Angew. Chem., Intern. Ed. Engl., 1, 600 (1962).

2. S.J. Brois, J. Am. Chem. Soc., 92, 1079 (1970).

3. A.B. Levy and H.C. Brown, J. Am. Chem. Soc., 95, 4067 (1973).

4. K. Harada and I. Nakamura, Chem. Commun., 13, 522 (1978).

5. A. Tassner, G.J. Matthews and F.W. Fowler, J. Am. Chem. Soc., 91, 5046 (1969).

6. G. Alvernhe and A. Laurent, J. Chem. Research(s), 23 (1978).

7. A. Hassner and C. Heathcock, J. Org. Chem., 30, 1748 (1965).

8. G. Snatzke and A. Veithen, Liebigs Ann., 159, 703 (1967).

9. M.J. Hairo and G.A. Boswell, J. Org. Chem., 42, 4231 (1977).

10. J.W. Ducker and S.C. Lazer, Aust. J. Chem., 23, 2535 (1970).

11. C.W. Shoppee, R.J. Bridgwater, D.N. Jones and G.H.R. Summers, J. Chem. Soc., 2492 (1956).

12. S.G. Levine and M.E. Wall, J. Am. Chem. Soc., 81, 2926 (1939).

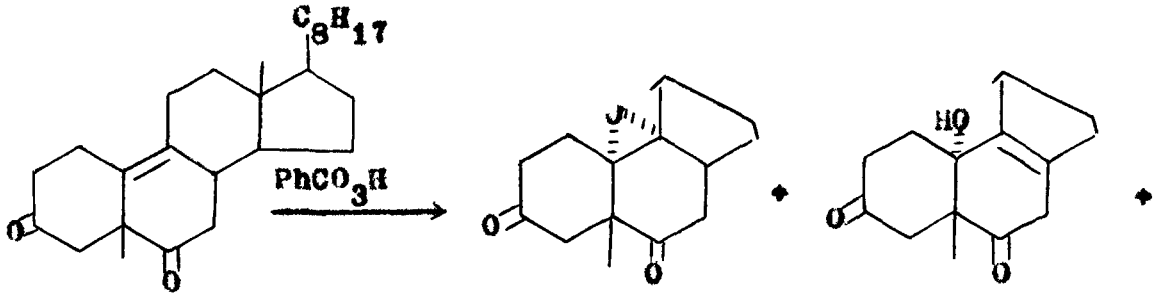
THESIS

Part - I

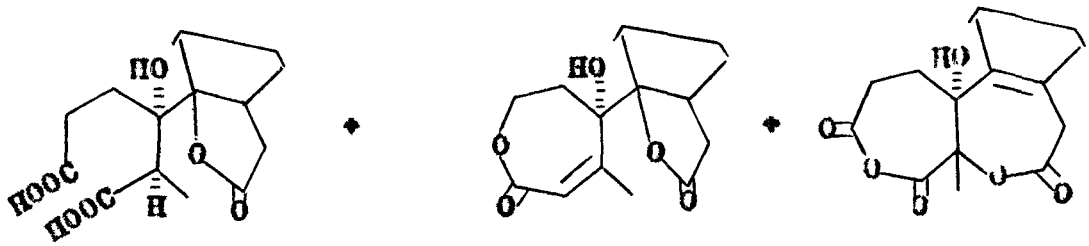
Baeyer-Villiger oxidation of steroidal ketones

The synthetic modification of steroids has been a major chemical endeavor in the past several decades. A number of papers on preparation of steroidal lactones, seco acids and rearranged products have appeared in literature. Some of the derivatives of 5,6-secosteroids have been shown to possess cytotoxic behaviour and are thus of possible interest as antitumor agents. In the present investigation, we subjected unexplored and easily accessible ketones such as, 5-methyl-19-nor-3β-cholest-9(10)-ene-3,6-dione (I), 3β-chloro-19-nor-5-methyl-3β-cholest-9(10)-en-6-one (II), 4,4-dimethylcholest-5-en-3-one (III), 4-methyl-cholest-4-en-3-one (IV) and its ethyl derivatives (V) and (VI) to Baeyer-Villiger oxidation in view to obtain interesting lactones and seco acids. The products obtained were characterized by their chemical and spectral studies.

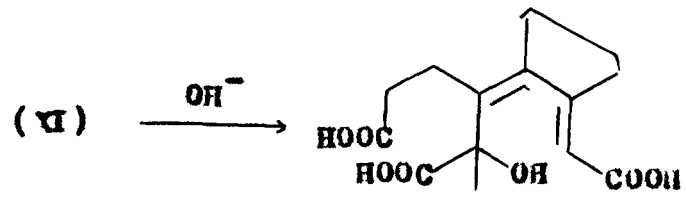
The ketone (I) under Baeyer-Villiger oxidation condition gave (VII), (VIII) along with abnormal products (IX), (X) and (XI). The subsequent hydrolysis of (XI) provided seco acid (XII). The ketone (II) afforded the compounds (XIII) and (XIV).



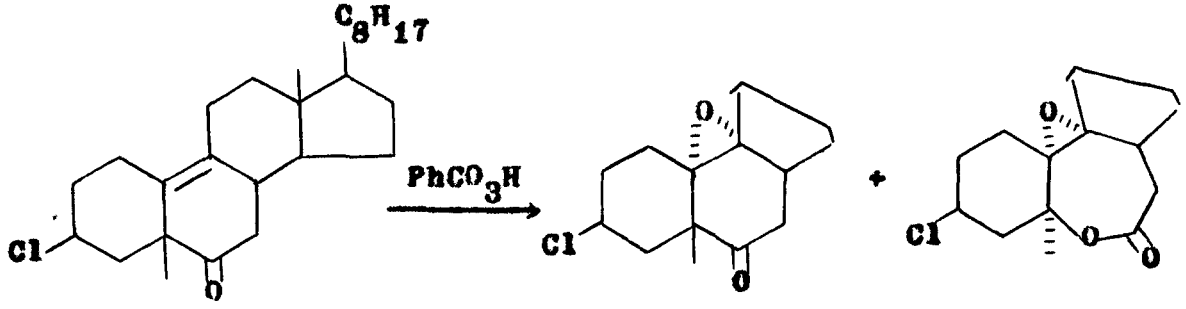
(I) (VII) (VIII)



(IX) (X) (XI)

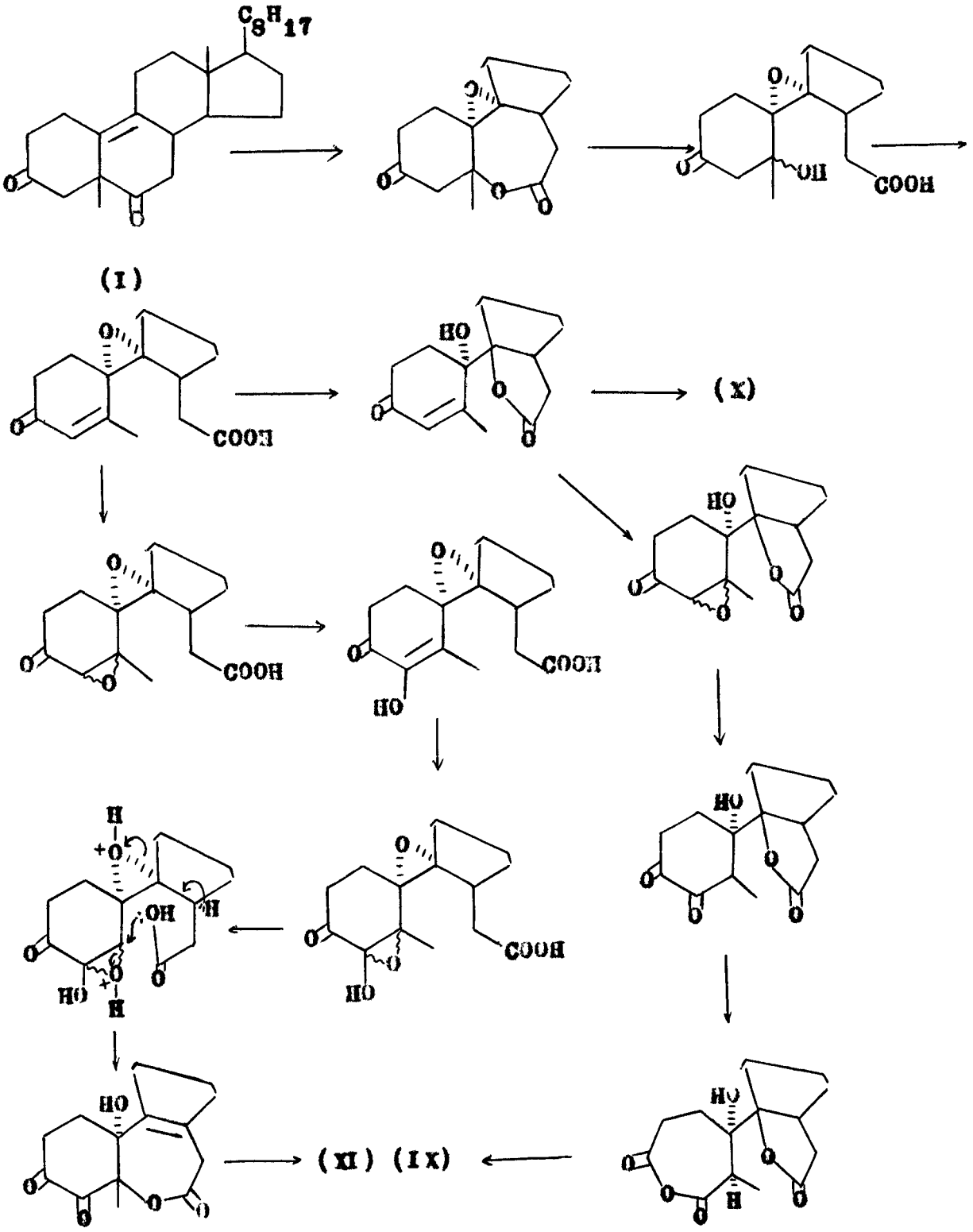


(XII)

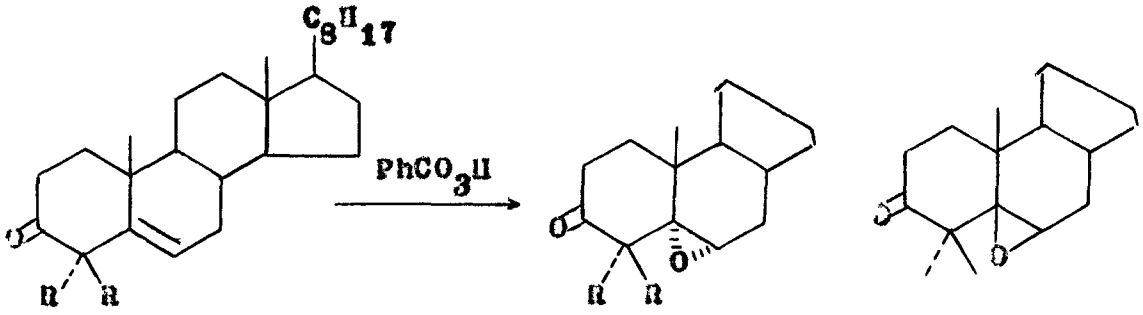


(II) (XIII) (XIV)

Formation of products (IX), (X) and (XI) can be explained according to the mechanism suggested as follows:



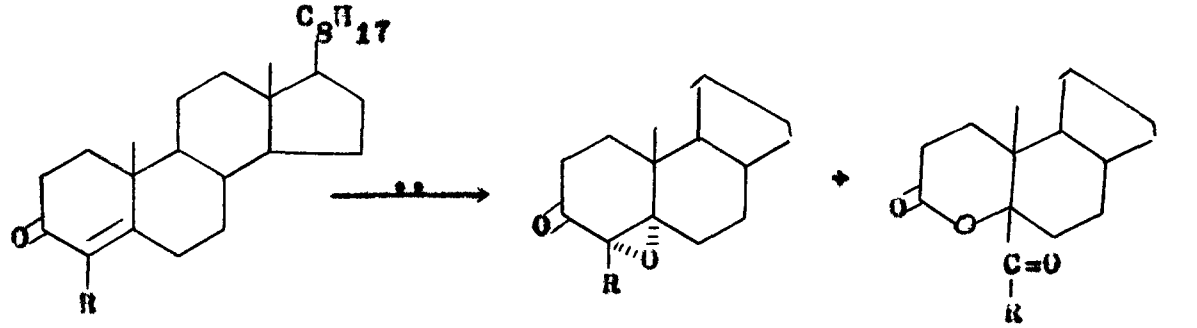
On similar treatment, with perbenzoic acid ketones (III-VI) gave the products which are given below:



	R
(III)	CH_3
(V)	C_2H_5

	R
(XV)	CH_3
(XX)	C_2H_5

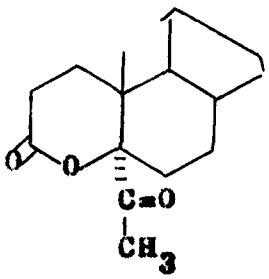
(XVI)



	R
(IV)	CH_3
(VI)	C_2H_5

	R
(XVII)	CH_3
(XXI)	C_2H_5

	R
(XIX)	CH_3
(XXII)	C_2H_5

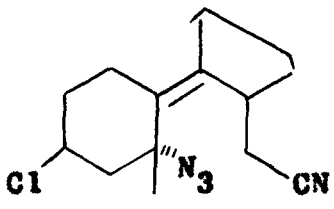


(XVIII)

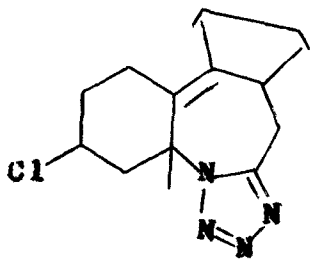
Part - II

Steroidal Tetrazoles

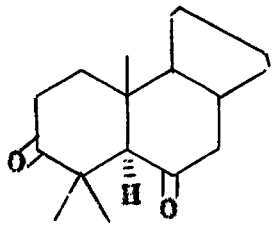
In the recent past, a number of steroidal tetrazoles were synthesized in our laboratory mainly pertaining to ring A and B which may be of potential lipolysis inhibitors. Further ettempts were made in present study to synthesize the steroidal tetrazoles derived from hitherto unexplored steroidal ketones such as (II), (III), (IV), (V) and (VI). The ketone (II) on treatment with excess of hydrazoic acid (BF_3-etherate catalyst) gave seco nitrile (XXIII)(abnormal product) and a tetrazole (XXIV) The ketone (III) on similar treatment gave diketone (XXV) and a tetrazole (XXVI) while (V) furnished seco nitrile (XXVII) and a tetrazole (XXVIII). Under identical reaction conditions, ketone (IV) yielded lactam (XXIX) and tetrazole (XXX) while (VI) gave isomeric tetrazoles (XXXI) and (XXXII).



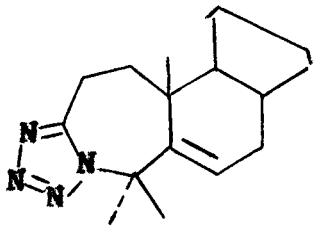
(XXIII)



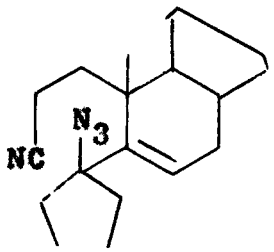
(XXIV)



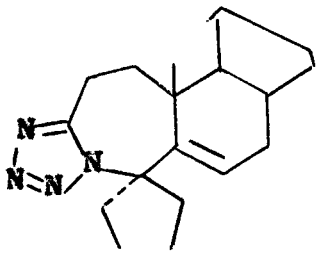
(XXV)



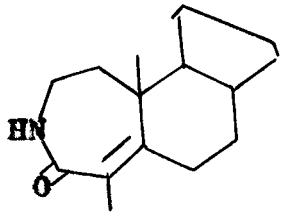
(XXVI)



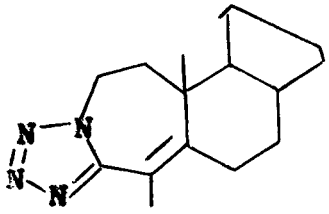
(XXVII)



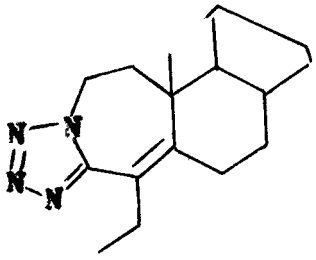
(XXVIII)



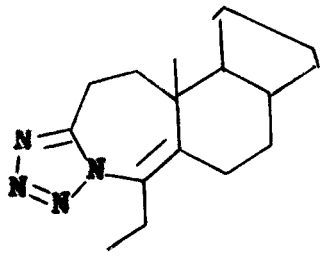
(XXIX)



(XXX)



(XXXI)

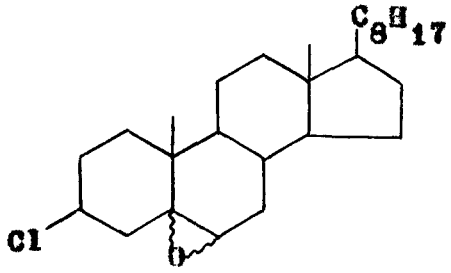


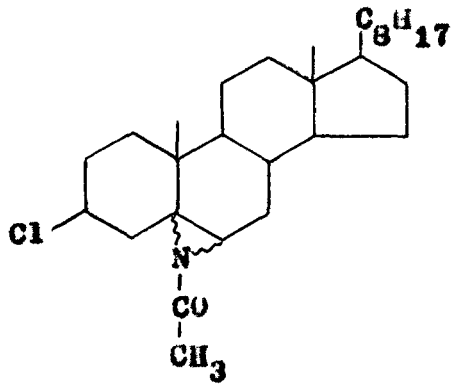
(XXXII)

Part - III

Synthesis of Steroidal aziridines

A number of papers appeared on the synthesis of aziridine in recent years and few of them are claimed to possess biological activity. This prompted us to synthesize new steroidal aziridines (XXXVII) and (XXXIX) from 3β-chloro-5,6α-epoxy-5α-cholestane (XXXIII) and its β -isomer (XXXIV) respectively which are worthy of biological testing.





(XXXIII) 5α,6α
(XXXIV) 5β,6β

(XXXVII) 5β,6β
(XXXIX) 5α,6α